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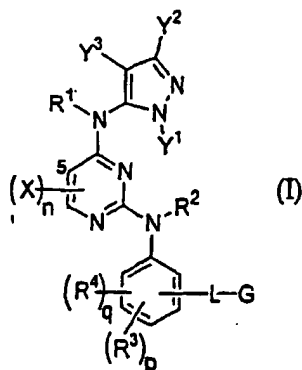
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(54) Title: 2-PHENYLAMINO-4-(5-PYRAZOLYLAMINO)-PYRIMIDINE DERIVATIVES AS KINASE INHIBITORS, IN PAR-
TICULAR, AS SRC KINASE INHIBITORS



(57) Abstract: The invention provides novel substituted 2,4-diaminopyrimidine compounds (I), in which L is a linker selected from: -O-(CH₂)₁₋₄-; s(O)₀₋₂-(CH₂)₁₋₄-; -N(R¹)-(CH₂)₁₋₄-(CH₂)₁₋₄-O-(CH₂)₁₋₄-; -N(R¹)-C(O)-(CH₂)₁₋₄-; (I) and (I) G represents: Alternatively, L may represent (I) or (I), and in this event, G represents (I) and pharmaceutical compositions thereof. The invention also provides methods of use of the novel substituted 2,4-diaminopyrimidine compounds and pharmaceutical compositions thereof as inhibitors of src kinase enzymes. Exemplary diseases that can be treated by the compounds of the invention include cell proliferative diseases, such as cancer and non-malignant cell proliferative diseases, osteoporosis and inflammatory diseases. Also provided are methods for preparing the compounds of the present invention.

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APPLICATION FOR PATENT

2-PHENYLAMINO-4-(5-PYRAZOLYLAMINO)-PYRIMIDINE DERIVATIVES AS KINASE INHIBITORS, IN PARTICULAR, AS SRC KINASE INHIBITORS

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Field of the Invention

The present invention relates to substituted pyrimidine compounds, and in particular, 2,4-diamine-substituted pyrimidine compounds, and pharmaceutical compositions thereof, and the use of such substituted pyrimidine compounds as inhibitors of src kinase enzymes.

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Background of the Invention

Normal tissue homeostasis is achieved by an intricate balance between the rate of cell proliferation and cell death. Disruption of this balance, e.g., by increasing the rate of cell proliferation, modulating the rate of cell differentiation or decreasing the rate of cell death, can result in the abnormal growth of cells and is thought to be a major event in the development of cancer, as well as other cell proliferative disorders such as restenosis.

Proliferative disorders, e.g., cancer, cause significant numbers of deaths. For example, cancer causes over half a million deaths per year in the United States alone. Conventional strategies for the treatment of cancer include chemotherapy, radiotherapy, surgery or combinations thereof, however further advances in these strategies are limited by lack of specificity and excessive toxicity to normal tissues. In addition, certain cancers are refractory to treatments such as chemotherapy, and some of these strategies such as surgery are not always viable alternatives. For example, non-small-cell lung cancer (NSCLC), which includes squamous cell carcinoma, adenocarcinoma and large-cell carcinoma, accounts for 75-80% of all lung cancers (American Cancer Society, 1993). Current multimodality therapeutic strategies applied to regionally advanced NSCLC are minimally effective with the overall cure rate being only about 10% (Belani (1993) Semin Oncol. 20:302 and Roth *et al.* (1994) Lung Cancer 11 Suppl 3:S25).

Cell growth, differentiation and other cell processes are regulated by signal transduction pathways involving protein phosphorylation. Protein phosphorylation is the

result of the transfer of a terminal phosphate of adenosine triphosphate to a particular amino acid of a protein. This transfer is catalyzed by enzymes termed kinases. Protein kinases comprise a large superfamily of homologous proteins. They are related by their kinase or catalytic domains, which consists of approximately 250-300 amino acid residues. There are
5 two main categories within the superfamily of protein kinases: the protein-serine/threonine kinases and the protein-tyrosine kinases (Hanks *et al.*, (1995) FASEB J. 9:576)

Kinases having an abnormal activity, e.g., mutated kinases, or abnormal levels of kinases, have been associated with abnormal cellular processes, which result in specific diseases. For example, several oncogenes, which are capable of transforming cells, are
10 mutated forms of normal genes encoding kinases. Examples of such oncogenes include the pp60-v-src gene from the Rous avian sarcoma virus, which corresponds to the normal (i.e., proto-oncogene) gene pp60-c-src, containing a deletion that removes the C-terminal 18 amino acids of c-src. Pp60-c-src is also referred to as "src kinase" or "src tyrosine kinase." Phosphorylation of a tyrosine residue at position 527 of c-src protein causes a great reduction
15 in its kinase activity, and this site is often altered in oncogenic derivatives of c-src (*see, e.g.*, Brown *et al.*, (1996) Biochem. Biophys. Acta 1287:121). Other proto-oncogenes encoding tyrosine kinases, which when mutated or over-expressed, cause cells to become transformed, include c-yes; c-fps (c-fes); c-abl and c-met. c-abl and c-met are associated with chronic myelogenous leukemia and osteosarcoma, respectively. Proto-oncogenes encoding
20 serine/threonine kinases include c-mos and c-raf (c-mil). Whereas the above-cited proto-oncogenes are intracellular transducers, other proto-oncogenes encode kinases which are cell-surface receptors. Examples of proto-oncogenes encoding cell surface receptors with tyrosine kinase activity include c-fms (or Colony Stimulating Factor -1 (CSF-1) receptor); c-erbB, which is an epidermal growth factor receptor; c-neu (or erbB-2), erbB-3 or erbB-4
25 which are related to epidermal growth factor receptor; and c-ros, which is related to the insulin receptor.

The role of abnormal kinase activity or protein levels in diseases has been abundantly documented. This has been demonstrated, e.g., by using inhibitors of kinases, in particular tyrosine kinases. Such inhibitors have been shown to be useful for the treatment of disease
30 states characterized by uncontrolled cell proliferation, e.g., cancer, inflammation, psoriasis, pulmonary fibrosis, glomerulonephritis, atherosclerosis, osteoporosis and restenosis following angioplasty. For example, tyrosine kinase inhibitors with selectivity for the EGF

receptor family have been shown to block tumor formation in animals, thus demonstrating their potential usefulness for directly suppressing tumor cell growth in the treatment of human cancer, especially breast carcinoma. Also, tumor metastasis and its associated angiogenesis has been shown to be inhibited by preventing the activation of the vascular endothelial growth factor receptor tyrosine kinase which indicates a utility for tyrosine kinase inhibitors in blocking separate events that occur during carcinogenesis. Thus, protein phosphorylation, e.g., tyrosine phosphorylation, plays an important role in cell regulatory processes, e.g., cell proliferation, and in diseases.

The pp60c-src protein has significant structural homology to about ten proteins (collectively referred to as Src Family kinases or SFKs) which include: Lck, Fyn, Yes, Yrk, Blk, Fgr, Hck, Lyn, and Frk subfamily members Frk/Rak and Iyk/Bsk (Sawyer *et al.*, (2001) Expert Opin. Investig. Drugs 10(7):1327). The Src family of tyrosine kinases, has three major domains: src homology SH1, SH2, and SH3 domains. The SH1 domain is most commonly called the catalytic domain or tyrosine kinase domain. The SH3 domain is a binding region for proteins having proline-rich sequences. Both the SH2 and SH3 domains are noncatalytic, but are important in protein-protein recognition. SH2 domains are homologous motifs of approximately 100 amino acids, which recognize and bind to the phosphorylated sequences present on regulatory proteins and growth factor receptors (Anderson *et al.*, *Science*, 1990, 250, 979).

One of the primary purposes of the src family phosphoprotein/SH2 domain interaction is to initiate the association of proteins into an activation complex, often around the intracellular domain of the receptor itself. This role of the src family SH2 domain mediates and organizes the ordered, physical assembly of the various proteins in the activation complex. The activity of a number of immunologically important src family SH2 domain-containing proteins, including, Fyn, Fgr, Yes, Lyn, Hck and Lck, is mediated in this way. P56lck is of particular interest because it has been associated with the signal transduction cascade needed for T-cell activation mediated by the T-cell receptor (TCR) (Straus *et al.* (1992) *Cell*, 70, 585).

The Src family of protein kinases, which all contain an SH2 domain, are involved in a number of cellular signalling pathways. For example, Src is involved in growth factor receptor signaling; integrin-mediated signaling; T- and B-cell activation; osteoclast activation; cell adhesion; cell motility and cell survival. It is known that the Src SH2 domain

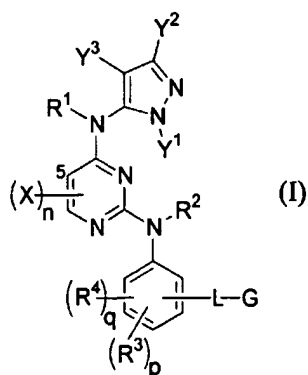
binds to several key receptor and nonreceptor tyrosine kinases such as tyrosine kinases containing receptors for PDGF, EGF, HER2/Neu (an oncogene form of EGF), Fibroblast Growth Factor (FGF), focal adhesion kinase, p130 protein, and p68 protein. In addition, src has been shown to be involved in the regulation of DNA synthesis, mitosis, and other cellular activities (*see, e.g., Susa et al. (2000) Trends Pharm. Sciences 21:489*).

Current cancer therapies utilize a battery of cytotoxic agents and radiation regimens to both decrease and eradicate tumors. The therapeutic index associated with these therapies is narrow and patients suffer from toxic side effects such as hair loss, bone marrow toxicity, loss of intestinal epithelium and mucositis. Many patients derive a therapeutic benefit from such treatment with an initial reduction in tumor mass and stabilization of the disease. However, recurrence is common and many times the tumors acquire a drug resistant phenotype and are refractory to future treatment with chemotherapeutic agents.

The need exists for kinase inhibitors, such as tyrosine kinase inhibitors, that overcome the above-mentioned deficiencies.

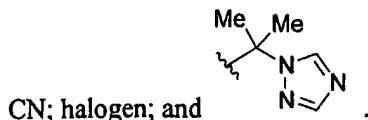
Summary of the Invention

This invention provides compounds for regulating cellular processes involving a kinase such as a tyrosine kinase, in particular, a src kinase. In its broad aspect, the invention relates to a compound of the formula (I)



in which Y^1 represents H, C_{1-4} alkyl, or phenyl optionally substituted up to three times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy. Y^2 and Y^3 are independently selected from H; C_{1-6} alkyl; C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl; phenyl optionally substituted up to three times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; adamantyl; CF_3 ; a 5-6 membered heteroaromatic containing up to two heteroatoms selected from N, O, and S, and optionally

substituted up to two times by halogen or C_{1-6} alkyl; $C(O)N(C_{1-4} \text{ alkyl})_2$; $C(O)O(C_{1-4} \text{ alkyl})$;



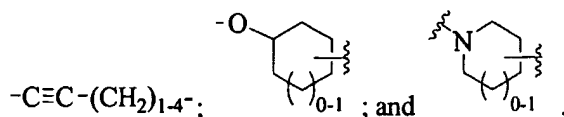
Alternatively, Y^2 and Y^3 are joined and together represent a fused aromatic ring optionally substituted up to two times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy.

- 5 X represents halogen or C_{1-4} alkyl. The subscript n represents 0, 1, or 2. R^1 represents H or C_{1-4} alkyl. R^2 represents H or C_{1-4} alkyl. R^3 represents: C_{1-6} alkyl; halogen; C_{1-4} alkoxy; O-phenyl optionally substituted up to two times by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, or di- $(C_{1-4} \text{ alkyl})$ amino; CN; or $N(R^1)_2$ wherein the R^1 moieties are independent or the R^1 moieties optionally are joined by a linker selected from the group consisting of
- 10 $CH(R^1)$, $N(R^1)$, S, $S(O)$, $S(O)_2$, and O, and taken together with the N to which they are attached, form a 5-6 membered nonaromatic heterocycle. The subscript p represents 0, 1, or 2. R^4 represents C_{1-4} alkyl or halogen, and q represents 0, 1, or 2.

Alternatively, R^3 and R^4 may be joined and taken together with the carbon atoms to which they are attached, form a 5-6 membered heteroaromatic ring containing up to two



15 heteroatoms selected from N, O, and S, and which is optionally substituted up to two times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy.

L is a linker selected from: $-O-(CH_2)_{1-4}-$; $-S(O)_{0-2}-(CH_2)_{1-4}-$; $-N(R^1)-(CH_2)_{1-4}-$; $-(CH_2)_{1-4}-O-(CH_2)_{1-4}-$; $-(CH_2)_{1-4}-$; $-N(R^1)-C(O)-(CH_2)_{1-4}-$;



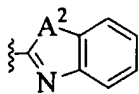
20 G represents:

- 1) NR^5R^6 , and a number of additional groups to be discussed below. In the substituent group NR^5R^6 , R^5 represents H, C_{1-6} alkyl, or C_{1-4} alkoxy- C_{1-4} alkyl. R^6 represents H; C_{1-6} alkyl; C_{1-4} alkoxy-substituted C_{1-4} alkyl; C_{5-6} cycloalkyl optionally substituted up to 2 times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; C_{3-6} cycloalkyl-substituted C_{1-4}
- 25 alkyl; benzyl; phenyl optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy,

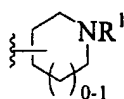
$-CO_2R^1$, $-C(O)N(R^1)_2$, $-N(R^1)_2$, or by a bivalent group , or . In the foregoing bivalent groups, A is $N(R^1)$, S, $S(O)$, $S(O)_2$, or O, and the bivalent group is

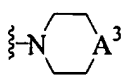
connected to the phenyl ring at adjacent carbon atoms to form a fused 5-membered

heterocycle. R^6 may also be $-(C_{1-4} \text{ alkyl})-N \text{---} A^1$, in which A^1 represents $N(R^1)$, S,

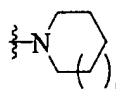
$S(O)$, $S(O)_2$, or O; or , in which A^2 represents $N(R^1)$, S, $S(O)$, $S(O)_2$, or O.

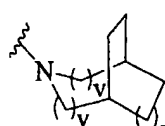
5 G may also be:

2) ₀₋₁, which may optionally be substituted up to 2 times by C_{1-3} alkyl, $(C_{1-3}$ alkoxy) $(C_{1-4}$ alkyl), $C(O)OR^1$, $C(O)N(R^1)_2$, phenyl, or benzyl;


3) ₀₋₁, which may optionally be substituted up to 2 times by C_{1-3} alkyl, $(C_{1-3}$ alkoxy) $(C_{1-4}$ alkyl), $C(O)OR^1$, $C(O)N(R^1)_2$, phenyl, or benzyl, and in which A^3 represents $N(R^1)$, S, $S(O)$, $S(O)_2$;

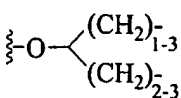
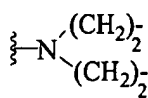
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4) ₀₋₁, which may optionally be substituted up to 2 times by oxo, $(C_{1-3}$ alkoxy) $-(C_{1-4}$ alkyl), $C(O)OR^1$, $C(O)N(R^1)_2$, phenyl, or benzyl, or up to 4 times by C_{1-3} alkyl; or

5) _v, which may optionally be substituted up to 2 times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy, and in which v is 0 or 1; or

15

6) ₀₋₁, which may optionally be substituted up to 2 times by C_{1-4} alkyl.

Alternatively, L may represent  or , and in this event,

G represents



20 Pharmaceutically acceptable salts are also within the scope of the invention.

In another aspect, the invention relates to a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

5 In yet another embodiment, the invention provides methods for regulating cellular processes involving a kinase, such as a tyrosine kinase. In a preferred embodiment, the cellular process involves a src kinase. The cellular process can be, e.g., cell proliferation or cell differentiation.

10 The invention provides methods for treating diseases associated with a kinase, e.g., diseases associated with an abnormal kinase activity or level, such as cancers, osteoporosis, and inflammatory disorders. The invention also provides methods for treating diseases associated with abnormal cell proliferation and/or differentiation. In a preferred embodiment, the method comprises administering to a subject in need thereof, a
15 pharmaceutically efficient amount of a compound of the invention, such that the subject is treated.

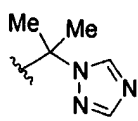
The invention also provides methods for preparing the compounds of the present invention. Also within the scope of the invention are kits comprising one or more
20 compounds of the invention, optionally in a pharmaceutical composition.

Detailed Description of the Invention

The invention is based at least in part on the observation that 2,4-diamino substituted pyrimidine compounds inhibit the activity of src kinases. Exemplary compounds are
25 described herein.

In formula (I), Y¹ is preferably H or C₁₋₄ alkyl, and more preferably H.

Preferably, Y² is selected from C₁₋₆ alkyl; C₃₋₆ cycloalkyl optionally substituted by C₁₋₄ alkyl; phenyl optionally substituted up to three times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy; adamantyl; CF₃; a 5-6 membered heteroaromatic containing up to two heteroatoms
30 selected from N, O, and S, and optionally substituted up to two times by halogen or C₁₋₆



alkyl; and Y^3 is H. As a preferred alternative, Y^2 and Y^3 are joined and together represent a fused aromatic ring optionally substituted up to two times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy.

More preferably, Y^2 is selected from C_{1-6} alkyl; C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl; phenyl optionally substituted up to three times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; adamantyl; and a 5-6 membered heteroaromatic containing up to two heteroatoms selected from N, O, and S, and optionally substituted up to two times by halogen or C_{1-6} alkyl; and Y^3 is H.

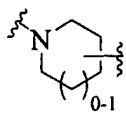
Most preferably, Y^2 is selected from C_{1-6} alkyl, and C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl; and Y^3 is H.

X preferably represents Cl, F, or C_{1-4} alkyl, and n is 0, 1, or 2. More preferably, X represents F, and n is 0 or 1.

The groups R^1 and R^2 are each preferably H.



R^3 is preferably C_{1-6} alkyl; halogen; C_{1-4} alkoxy; CN; or $N(R^1)_2$ in which the R^1 moieties are independent, or the R^1 moieties optionally are joined by a linker selected from the group consisting of $CH(R^1)$, $N(R^1)$, S, $S(O)$, $S(O)_2$, and O, and taken together with the N to which they are attached, form a 5-6 membered nonaromatic heterocycle. More preferably, R^3 is C_{1-6} alkyl; C_{1-4} alkoxy; CN; or $N(R^1)_2$ in which the R^1 moieties are independent, or the R^1 moieties optionally are joined by a linker selected from the group consisting of $CH(R^1)$, $N(R^1)$, S, $S(O)$, $S(O)_2$, and O, and taken together with the N to which they are attached, form a 5-6 membered nonaromatic heterocycle. Most preferably, R^3 is C_{1-6} alkyl; C_{1-4} alkoxy; or $N(R^1)_2$ in which the R^1 moieties are independent, or the R^1 moieties optionally are joined by a linker selected from the group consisting of $CH(R^1)$, $N(R^1)$, S, $S(O)$, $S(O)_2$, and O, and taken together with the N to which they are attached, form a 5-6 membered nonaromatic heterocycle. The subscript p, which represents the number of R^3 groups, is preferably 0, 1, or 2, more preferably 0 or 1. Preferably, the phenyl ring of Fig. (I) bears no R^4 groups.

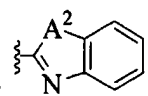
L is preferably $-O-(CH_2)_{1-4}-$; $-S(O)_{0-2}-(CH_2)_{1-4}-$; $-N(R^1)-(CH_2)_{1-4}-$; $-(CH_2)_{1-4}-$; $-(CH_2)_{1-4}-O-(CH_2)_{1-4}-$; $-(CH_2)_{1-4}-N(R^1)-(CH_2)_{1-4}-$; or $-N(R^1)-C(O)-(CH_2)_{1-4}-$.

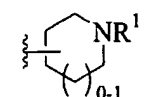


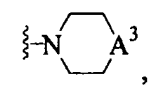
G is preferably:

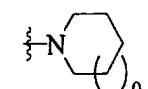
- 1) NR^5R^6 , in which R^5 represents H or C_{1-6} alkyl; and R^6 represents: C_{1-6} alkyl; C_{1-4} alkoxy-substituted C_{1-4} alkyl; C_{5-6} cycloalkyl optionally substituted up to 2 times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; C_{3-6} cycloalkyl-substituted C_{1-4} alkyl; benzyl; phenyl optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, $-\text{CO}_2\text{R}^1$,

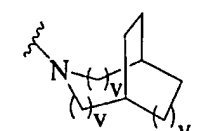
5 $-\text{C}(\text{O})\text{N}(\text{R}^1)_2$, $-\text{N}(\text{R}^1)_2$, or by a bivalent group , or  in which A is $\text{N}(\text{R}^1)$, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, or O, and this bivalent group is connected to the phenyl ring at

adjacent carbon atoms to form a fused 5-membered heterocycle; or , in which A^2 represents $\text{N}(\text{R}^1)$, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, or O;

- 2) ₀₋₁, optionally substituted up to 2 times by C_{1-3} alkyl, $(\text{C}_{1-3}$ alkoxy)(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl;

- 3) ₀₋₁, optionally substituted up to 2 times by C_{1-3} alkyl, $(\text{C}_{1-3}$ alkoxy)(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl, and in which A^3 represents $\text{N}(\text{R}^1)$, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, or O;


- 4) ₀₋₁, optionally substituted up to 2 times by oxo, $(\text{C}_{1-3}$ alkoxy)-(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl, or up to 4 times by C_{1-3} alkyl; or

- 5) _v, optionally substituted up to 2 times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy, and in which v is 0 or 1.

L is more preferably $-\text{O}-(\text{CH}_2)_{1-4}-$; $-\text{S}(\text{O})_{0-2}-(\text{CH}_2)_{1-4}-$; $-\text{N}(\text{R}^1)-(\text{CH}_2)_{1-4}-$; $-(\text{CH}_2)_{1-4}-$
 20 $\text{O}-(\text{CH}_2)_{1-4}-$; or $-\text{N}(\text{R}^1)-\text{C}(\text{O})-(\text{CH}_2)_{1-4}-$.

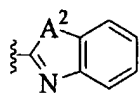
G is more preferably

- 1) NR^5R^6 , in which R^5 represents H or C_{1-6} alkyl; and R^6 represents C_{1-6} alkyl; C_{5-6} cycloalkyl optionally substituted up to 2 times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; benzyl; phenyl optionally substituted by halogen, C_{1-4} alkyl,

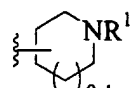
C_{1-4} alkoxy, $-CO_2R^1$, $-C(O)N(R^1)_2$, $-N(R^1)_2$, or by a bivalent group , or

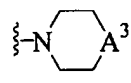


in which A is $N(R^1)$, S, $S(O)$, $S(O)_2$, or O, and this bivalent group is connected to the phenyl ring at adjacent carbon atoms to form a fused 5-

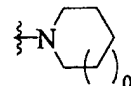
membered heterocycle; or , in which A^2 represents $N(R^1)$, S, $S(O)$, $S(O)_2$, or O;

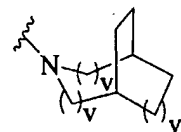
5

2) ₀₋₁, optionally substituted up to 2 times by C_{1-3} alkyl, $(C_{1-3}$ alkoxy)(C_{1-4} alkyl), $C(O)OR^1$, $C(O)N(R^1)_2$, phenyl, or benzyl;

3) ₀₋₁, optionally substituted up to 2 times by C_{1-3} alkyl, $(C_{1-3}$ alkoxy)(C_{1-4} alkyl), $C(O)OR^1$, $C(O)N(R^1)_2$, phenyl, or benzyl, and in which A^3 represents $N(R^1)$, S, $S(O)$, $S(O)_2$, or O;

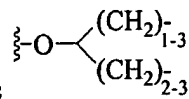

10

4) ₀₋₁, optionally substituted up to 2 times by oxo, $(C_{1-3}$ alkoxy)-(C_{1-4} alkyl), $C(O)OR^1$, $C(O)N(R^1)_2$, phenyl, or benzyl, or up to 4 times by C_{1-3} alkyl;

5) _v, optionally substituted up to 2 times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy, and in which v is 0 or 1.

15

A preferred combination of L and G groups is when

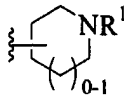
L represents  and G represents .

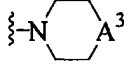
20

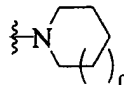
Most preferably, L is $-O-(CH_2)_{1-4}-$; $-N(R^1)-(CH_2)_{1-4}-$; or $-(CH_2)_{1-4}-O-(CH_2)_{1-4}-$.

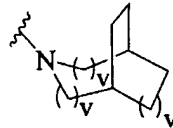
Most preferably, G is:

- 1) NR^5R^6 , in which R^5 represents H or C_{1-6} alkyl; and R^6 represents C_{1-6} alkyl; C_{5-6} cycloalkyl optionally substituted up to 2 times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

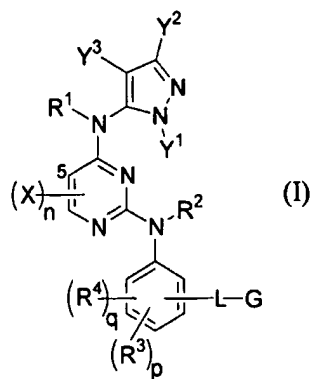
- 2) , optionally substituted up to 2 times by C_{1-3} alkyl, (C_{1-3} alkoxy)(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl;

- 3) , optionally substituted up to 2 times by C_{1-3} alkyl, (C_{1-3} alkoxy)(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl, and in which A^3 represents $\text{N}(\text{R}^1)$, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, or O;

- 4) , optionally substituted up to 2 times by oxo, (C_{1-3} alkoxy)-(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl, or up to 4 times by C_{1-3} alkyl;

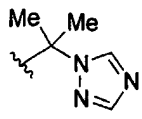
- 5) , optionally substituted up to 2 times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy, and in which v is 0 or 1.

In a preferred embodiment, compounds of the invention have the formula (I)



Y^1 represents H or C_{1-4} alkyl. Y^2 is selected from C_{1-6} alkyl; C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl; phenyl optionally substituted up to three times by halogen, C_{1-4}

alkyl, or C₁₋₄ alkoxy; adamantyl; CF₃; a 5-6 membered heteroaromatic containing up to two heteroatoms selected from N, O, and S, and optionally substituted up to two times by



halogen or C₁₋₆ alkyl; and ; and Y³ is H. Alternatively, Y² and Y³ are joined and together represent a fused aromatic ring optionally substituted up to two times by halogen,

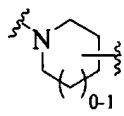
5 C₁₋₄ alkyl, or C₁₋₄ alkoxy.

X represents Cl, F, or C₁₋₄ alkyl; and n represents 0, 1, or 2.

In this embodiment, R¹ and R² each represents H.

R³ represents C₁₋₆ alkyl; halogen; C₁₋₄ alkoxy; CN, or N(R¹)₂ in which the R¹ moieties are independent, or the R¹ moieties optionally are joined by a linker selected from
10 the group consisting of CH(R¹), N(R¹), S, S(O), S(O)₂, and O, and taken together with the N to which they are attached, form a 5-6 membered nonaromatic heterocycle. The subscript p represents 0, 1, or 2. The subscript q, representing the number of R⁴ groups, is 0.

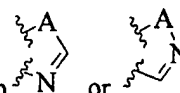

L is a linker selected from -O-(CH₂)₁₋₄- ; -S(O)₀₋₂-(CH₂)₁₋₄- ; -N(R¹)-(CH₂)₁₋₄- ;

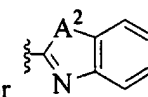


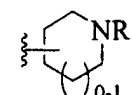
0-1 ; -(CH₂)₁₋₄-O-(CH₂)₁₋₄- ; -(CH₂)₁₋₄- ; and -N(R¹)-C(O)-(CH₂)₁₋₄- .

15 G represents:

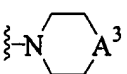
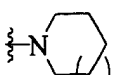
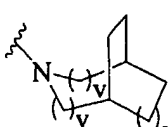
- 1) NR⁵R⁶, in which R⁵ represents H or C₁₋₆ alkyl; and R⁶ represents C₁₋₆ alkyl; C₁₋₄ alkoxy-substituted C₁₋₄ alkyl; C₃₋₆ cycloalkyl optionally substituted up to 2 times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy; C₃₋₆ cycloalkyl-substituted C₁₋₄ alkyl; benzyl; phenyl optionally substituted by halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, -CO₂R¹,

20 -C(O)N(R¹)₂, -N(R¹)₂, or by a bivalent group , or  in which A is N(R¹), S, S(O), S(O)₂, or O, and this bivalent group is connected to the phenyl ring at

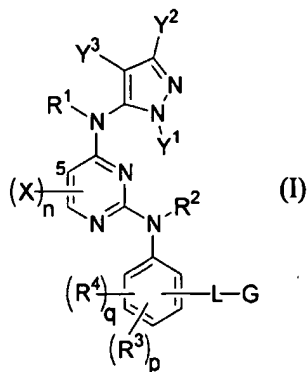
adjacent carbon atoms to form a fused 5-membered heterocycle; or , in which A² represents N(R¹), S, S(O), S(O)₂, or O;

- 2) ₀₋₁, optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl;

25

- 3) , optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, and wherein A³ represents N(R¹), S, S(O), S(O)₂, or O;
- 4) , optionally substituted up to 2 times by oxo, (C₁₋₃ alkoxy)-(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, or up to 4 times by C₁₋₃ alkyl;
- 5) , optionally substituted up to 2 times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy, and in which v is 0 or 1.

In a more preferred embodiment, compounds of the invention have the formula (I)



in which

- Y¹ represents H. Y² is selected from C₁₋₆ alkyl; C₃₋₆ cycloalkyl optionally substituted by C₁₋₄ alkyl; phenyl optionally substituted up to three times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy; adamantyl, a 5-6 membered heteroaromatic containing up to two heteroatoms selected from N, O, and S, and optionally substituted up to two times by halogen or C₁₋₆ alkyl. Y³ is H.

X represents F; and n represents 0 or 1.



- R¹ and R² each represents H. R³ represents C₁₋₆ alkyl; C₁₋₄ alkoxy; CN; or N(R¹)₂ wherein the R¹ moieties are independent, or the R¹ moieties optionally are joined by a linker selected from the group consisting of CH(R¹), N(R¹), S, S(O), S(O)₂, and O, and taken together with the N to which they are attached, form a 5-6 membered nonaromatic

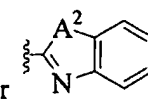
heterocycle; and p represents 0 or 1. The subscript q, representing the number of R⁴ groups, is 0.

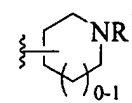
L is a linker selected from -O-(CH₂)₁₋₄- ; -S(O)₀₋₂-(CH₂)₁₋₄- ; -N(R¹)-(CH₂)₁₋₄- ; -(CH₂)₁₋₄-O-(CH₂)₁₋₄- ; and -N(R¹)-C(O)-(CH₂)₁₋₄- .

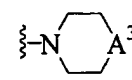
5 G represents:

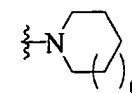
- 1) NR⁵R⁶ , in which R⁵ represents H or C₁₋₆ alkyl; and R⁶ represents C₁₋₆ alkyl; C₅₋₆ cycloalkyl optionally substituted up to 2 times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy; benzyl; phenyl optionally substituted by halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, -CO₂R¹,

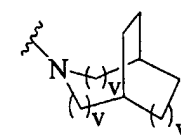
10 -C(O)N(R¹)₂ , -N(R¹)₂ , or by a bivalent group , or  in which A is N(R¹), S, S(O), S(O)₂, or O , and this bivalent group is connected to the phenyl ring at

adjacent carbon atoms to form a fused 5-membered heterocycle; or  , in which A² represents N(R¹), S, S(O), S(O)₂ , or O;

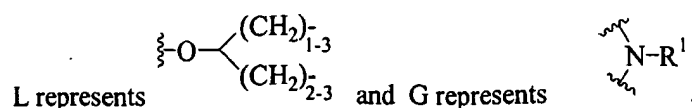
- 2) ₀₋₁ , optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂ , phenyl, or benzyl;

15 3) ₀₋₁ , optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂ , phenyl, or benzyl, and in which A³ represents N(R¹), S, S(O), S(O)₂ , or O;

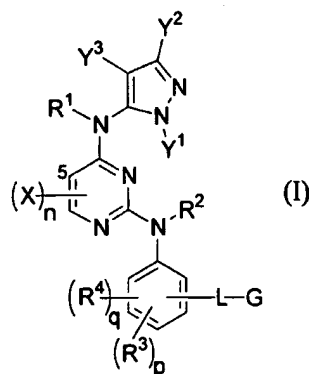
- 4) ₀₋₁ , optionally substituted up to 2 times by oxo, (C₁₋₃ alkoxy)-(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂ , phenyl, or benzyl, or up to 4 times by C₁₋₃ alkyl;

20 5) _v , optionally substituted up to 2 times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy, and wherein v is 0 or 1.

or



In the most preferred embodiment, compounds of the invention have the formula (I)



in which

Y^1 represents H. Y^2 is C_{1-6} alkyl, or C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl. Y^3 is H.

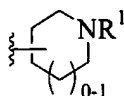
X represents F; and n represents 0 or 1.

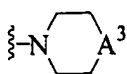
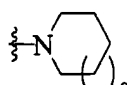
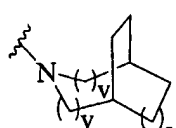
R^1 and R^2 each represents H. R^3 represents C_{1-6} alkyl; C_{1-4} alkoxy, or $N(R^1)_2$ in which the R^1 moieties are independent, or the R^1 moieties optionally are joined by a linker selected from the group consisting of $CH(R^1)$, $N(R^1)$, S, $S(O)$, $S(O)_2$, and O, and taken together with the N to which they are attached, form a 5-6 membered nonaromatic heterocycle. The subscript p, representing the number of R^3 groups, is 0 or 1. The subscript q, representing the number of R^4 groups, is 0.

L is a linker selected from $-O-(CH_2)_{1-4}-$; $-N(R^1)-(CH_2)_{1-4}-$; and $-(CH_2)_{1-4}-O-(CH_2)_{1-4}-$.

G represents:

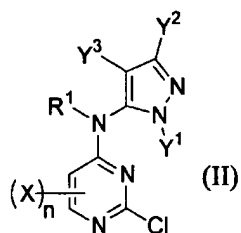
1) NR^5R^6 , in which R^5 is H or C_{1-6} alkyl; and R^6 represents C_{1-6} alkyl, or C_{5-6} cycloalkyl optionally substituted up to 2 times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

2) , optionally substituted up to 2 times by C_{1-3} alkyl, $(C_{1-3}$ alkoxy)(C_{1-4} alkyl), $C(O)OR^1$, $C(O)N(R^1)_2$, phenyl, or benzyl;

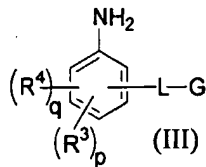
- 3) , optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, and in which A³ represents N(R¹), S, S(O), S(O)₂, or O;
- 4) ₀₋₁, optionally substituted up to 2 times by oxo, (C₁₋₃ alkoxy)-(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, or up to 4 times by C₁₋₃ alkyl; or
- 5) _v, optionally substituted up to 2 times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy, and in which v is 0 or 1.

When present, the group X in the middle ring is preferably on the C-5 position of the pyrimide. Also, in the lower ring, the L-G group is preferably *meta* to the amino N.

The compounds of formula (I) are generally made by coupling a compound of formula (II)



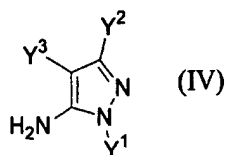
with a compound of formula (III)



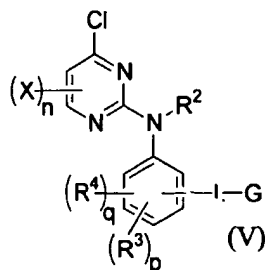
, and, in the case where R² is an alkyl group, alkylating the resulting secondary amine, to yield a compound of formula (I);

or

coupling a compound of formula (IV)



with a compound of formula (V)



and, in the case where R¹ is an alkyl group, alkylating

the resulting secondary amine, to yield a compound of formula (I).

- 5 In formulae (II), (III), (IV), and (V), the meanings of the substituent groups are as described above.

Examples of 5-6 membered heteroaromatics containing up to two heteroatoms selected from N, O, and S and employed for groups Y² or Y³ in formula (I) include, but are not limited to, pyridinyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, furanyl, pyrrolyl,
10 thiazolyl, or thienyl.

When R¹ moieties of a group N(R¹)₂ are referred to as “independent” it is meant that they are separate groups, each being joined to the N but not joined to each other.

When the R¹ moieties of a group N(R¹)₂ are referred to as being joined by a linker selected from the group consisting of CH(R¹), N(R¹), S, S(O), S(O)₂, and O, and taken
15 together with the N to which they are attached, form a 5-6 membered nonaromatic heterocycle, cyclic moieties such as morpholine, thiomorpholine, pyrrolidine, piperidine, or piperazine are contemplated.

When it is stated that R³ and R⁴ may be joined and taken together with the carbon atoms to which they are attached, form a 5-6 membered heteroaromatic ring containing up to
20 two heteroatoms selected from N, O, and S, moieties such as pyridine, pyrimidine, thiazole, imidazole, pyrrole, furan, or thiophene are contemplated.

Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The terms "a" and "an" refer to "one or more" when used in this application, including the claims.

5 "Abnormal growth of cells" means cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition).

The term "analog" of a compound refers to a compound having a substantial structural similarity to a particular compound and having essentially the same type of biological activity as the compound.

10 The term "antiproliferative" therapeutic or compound refers to a compound or therapeutic which inhibits cell proliferation to at least some extent.

The term "cytostatic" when referring to the activity of a compound means that the compound causes the cell to cell cycle arrest, but it does not kill the cell. Thus, removal of the drug from the environment of the cell results in the resumption of cell proliferation.

15 The term "derivative" of a compound or of a small molecule refers to a compound which can be derived, e.g., by chemical synthesis, from the original compound. Thus a derivative of a compound has certain structural similarities with the compound.

"Disease associated with an abnormal activity or level of a kinase" refers to a disease in which an abnormal activity or protein level of a kinase is present in certain cells, and in
20 which the abnormal activity or protein level of the kinase is at least partly responsible for the disease.

A "disease associated with a kinase" refers to a disease that can be treated with a kinase inhibitor.

"Diseases associated with src kinase-mediated signaling" refers to diseases which can
25 be treated with an inhibitor of src kinase-mediated signaling. Such disease can, e.g., be associated with an abnormal src kinase activity or level.

The terms "excessive cell proliferation," used interchangeably herein with "hyper-proliferation" of cells refers to cells which divide more often than their normal or wild-type counterpart. Thus, cells are excessively proliferating when they double in less than 24 hours
30 if their normal counterparts double in 24 hours. Excessive proliferation can be detected by simple counting of the cells, with or without specific dyes, or by detecting DNA replication

or transcription, such as by measuring incorporation of a labeled molecule or atom into DNA or RNA.

“Inhibiting cell proliferation” refers to decreasing the rate of cell division, by interrupting or slowing down the cell cycle. The term refers to complete blockage of cell proliferation, i.e., cell cycle arrest, as well as to a lengthening of the cell cycle. For example, the period of a cell cycle can be increased by about 10%, about 20%, about 30, 40, 50, or 100%. The duration of the cell cycle can also be augmented by a factor of two, three, 4, 5, 10 or more.

“Modulating cell differentiation” refers to the stimulation or inhibition of cell differentiation.

“Normalizing cell proliferation” refers to reducing the rate of cell proliferation of a cell that proliferates excessively relative to that of its normal or wild-type counterpart, or increasing the rate of cell proliferation of a cell that proliferates poorly relative to its normal or wild-type counterpart.

A “patient” or “subject” to be treated by the subject method can mean either a human or non-human animal.

The term “proliferative disorder” refers to any disease/disorder of a tissue marked by unwanted or aberrant proliferation of at least some cells in the tissue. Such diseases include cancer, as well as benign diseases or disorders, such as warts or other benign tumors.

A “src inhibitor” is a compound which inhibits at least part of the activity of a src kinase in a cell. The inhibition can be, at least about 20%, preferably at least about 40%, even more preferably at least about 50%, 70%, 80%, 90%, 95%, and most preferably at least about 98% of the activity of the src kinase.

“Treating” a disease refers to preventing, curing or improving at least one symptom of a disease.

The following definitions pertain to the structure of the compounds:

The abbreviations Me, Et, Ph, and OMe represent methyl, ethyl, phenyl, and methoxy respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry* (i.e. *J. Org. Chem.* **1995**, 60, 12a.). This list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in this list are hereby incorporated by reference.

"Alkyl" means a hydrocarbon radical having up to a maximum of 12 carbon atoms, which may be linear or branched with single or multiple branching. Alkyl is especially lower alkyl. Examples of such alkyl groups are methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, and isohexyl.

5 "Halogen" means fluorine, chlorine, bromine, or iodine but is especially fluorine, chlorine, or bromine.

"Cycloalkyl" is a saturated carbocycle that contains between 3 and 12 carbons but preferably 3 to 8 carbons. Examples include the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups.

10 The term "alkoxy" means a group in which the alkyl portion is straight or branched and has the designated number of carbon atoms. Examples of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, and isohexoxy.

The term "optionally" means that the subsequent described event(s) may or may not
15 occur, and includes both event(s), which occur, and event(s) that do not occur.

The term "oxo" refers to the group =O.

Abbreviations and Acronyms

20 When the following abbreviations are used throughout the disclosure, they have the following meaning:

ADDP	1,1'-(azodicarbonyl)dipiperidine
ATP	adenosine triphosphate
Ar	argon
25 BRIJ	polyoxyethylene(23) lauryl ether
BSA	bovine serum albumin
n-BuOH	1-butanol
CBr ₄	carbon tetrabromide
CD ₃ OD	methanol- <i>d</i> ₄
30 CDCl ₃	chloroform- <i>d</i>
CH ₂ Cl ₂	methylene chloride
CH ₃ CN	acetonitrile

	Cs ₂ CO ₃	cesium carbonate
	Cu(OTf) ₂ ·Ph	copper(I) trifluoromethanesulfonate benzene complex
	DEAD	diethyl azodicarboxylate
	DMF	dimethylformamide
5	DMSO	dimethylsulfoxide
	EDTA	ethylenediaminetetraacetic acid
	ESI-MS	electrospray-mass spectrometry ionization
	EtOAc	ethyl acetate
	Et ₂ O	diethyl ether
10	Et ₃ N	triethylamine
	H ₂	hydrogen gas
	HBr	hydrobromic acid
	HCl	hydrochloric acid
	HEPES	4-(2-hydroxyethyl)-1-piperazineethane-sulfonic acid
15	HEX	hexanes
	¹ H NMR	proton nuclear magnetic resonance
	HPLC	high pressure liquid chromatography
	Hz	hertz
	K ₂ CO ₃	potassium carbonate
20	KOAc	potassium acetate
	KOH	potassium hydroxide
	LC/MS	liquid chromatography / mass spectrometry
	MeOH	methanol
	MgSO ₄	anhydrous magnesium sulfate
25	MMTV	murine mammary tumor virus
	MPLC	medium pressure liquid chromatography
	MS ES	mass spectroscopy with electrospray
	NaH	sodium hydride
	NaHCO ₃	sodium bicarbonate
30	NaI	sodium iodide
	NaOH	sodium hydroxide
	P ₂ O ₅	phosphorous pentoxide

	POCl ₃	phosphorous oxychloride
	Poly-GAT	poly glycine, alanine, tyrosine
	PPh ₃	triphenyl phosphine
	RNA	ribonucleic acid
5	rt	room temperature
	SnCl ₂	tin(II) chloride
	Streptavidin-APC	streptavidin conjugated allopyrocyanin
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
10	TLC	thin layer chromatography

Compounds of the Invention

The present invention provides substituted pyrimidine compounds, e.g., 2,4-diamino substituted pyrimidine compounds, which are capable of inhibiting src kinase activity.

15 Exemplary compounds of the invention have the IUPAC name set forth below:

Example	IUPAC NAME
1	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
2	4-({4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl} amino)-2-[2-(diethylamino)ethoxy]benzonitrile
3	4-({4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl} amino)-2-[2-(diethylamino)ethoxy]benzonitrile
4	<i>N</i> ² -{3-[2-(diethylamino)ethoxy]phenyl}- <i>N</i> ⁴ -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
5	<i>N</i> ² -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- <i>N</i> ⁴ -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
6	<i>N</i> ² -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-5-fluoro- <i>N</i> ⁴ -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
7	2-[2-(diethylamino)ethoxy]-4-({4-[(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl} amino)benzonitrile
8	<i>N</i> ² -{4-methoxy-3-[2-(1-pyrrolidinyl)ethoxy]phenyl}- <i>N</i> ⁴ -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
9	5-fluoro- <i>N</i> ² -{4-methoxy-3-[2-(1-pyrrolidinyl)ethoxy]phenyl}- <i>N</i> ⁴ -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine

10	N^4 -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
11	N^2 -{4-methoxy-3-[2-(1-piperidinyl)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
12	5-fluoro- N^2 -{4-methoxy-3-[2-(1-piperidinyl)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
13	N^2 -{3-[2-(4-methyl-1-piperidinyl)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
14	N^2 -{3-[(1-methyl-3-piperidinyl)methoxy]phenyl}- N^4 -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
15	N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
16	N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
17	N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]-5-fluoro-2,4-pyrimidinediamine
18	2-[2-(diethylamino)ethoxy]-4-[(4-{[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]amino}-2-pyrimidinyl)amino]benzonitrile
19	N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{4-methoxy-3-[2-(1-pyrrolidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
20	N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]-5-fluoro- N^2 -{4-methoxy-3-[2-(1-pyrrolidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
21	N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{3-[2-(1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
22	N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{4-methoxy-3-[2-(1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
23	N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]-5-fluoro- N^2 -{4-methoxy-3-[2-(1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
24	N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{3-[2-(4-methyl-1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
25	N^2 -(3-{2-[(3 <i>R</i> ,5 <i>S</i>)-3,5-dimethyl-1-piperidinyl]ethoxy}phenyl)- N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-

	pyrimidinediamine
26	N^2 -(3-{2-[(3 <i>R</i> ,5 <i>S</i>)-3,5-dimethyl-1-piperidinyl]ethoxy}-4-methylphenyl)- N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
27	N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{3-[(1-methyl-3-piperidinyl)methoxy]phenyl}-2,4-pyrimidinediamine
28	N^4 -(3-cyclopropyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[(1-methyl-3-piperidinyl)methoxy]phenyl}-2,4-pyrimidinediamine
29	N^4 -(3-cyclopropyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -{3-[(1-methyl-3-piperidinyl)methoxy]phenyl}-2,4-pyrimidinediamine
30	N^2 -{3-[2-(benzylamino)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-methyl-2,4-pyrimidinediamine
31	N^2 -{3-[2-(benzylamino)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
32	N^2 -{3-[2-(benzylamino)ethoxy]phenyl}-5-bromo- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
33	N^2 -(3-{2-[benzyl(2-methoxyethyl)amino]ethoxy}phenyl)- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
34	N^2 -{4-bromo-3-[2-(diethylamino)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
35	N^2 -{4-bromo-3-[2-(diethylamino)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro-2,4-pyrimidinediamine
36	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(4-fluorophenyl)amino]ethoxy}phenyl)-2,4-pyrimidinediamine
37	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -(3-{2-[(4-fluorophenyl)amino]ethoxy}phenyl)-2,4-pyrimidinediamine
38	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(4-methoxyphenyl)amino]ethoxy}phenyl)-2,4-pyrimidinediamine
39	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -(3-{2-[(4-methoxyphenyl)amino]ethoxy}phenyl)-2,4-pyrimidinediamine
40	N^2 -{3-[6-(3 <i>H</i> -benzthiazol-2-ylamino)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
41	N^2 -{3-[2-(1 <i>H</i> -benzimidazol-2-ylamino)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
42	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(1 <i>H</i> -indazol-5-ylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
43	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(1 <i>H</i> -indazol-5-ylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
44	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -{3-[2-(1 <i>H</i> -indazol-

	5-ylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
45	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(4-methyl-1-piperazinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
46	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-methyl- N^2 -{3-[2-(4-methyl-1-piperazinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
47	5-bromo- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-methyl- N^2 -{3-[2-(4-methyl-1-piperazinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
48	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(2 <i>R</i>)-2-(methoxymethyl)-1-pyrrolidinyl]ethoxy}phenyl)-2,4-pyrimidinediamine
49	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(3 <i>R</i> ,5 <i>S</i>)-3,5-dimethyl-1-piperidinyl]ethoxy}phenyl)-2,4-pyrimidinediamine
50	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(3 <i>R</i> ,5 <i>S</i>)-3,5-dimethyl-1-piperidinyl]ethoxy}phenyl)-5-fluoro-2,4-pyrimidinediamine
51	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(cyclohexylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
52	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(cyclohexylamino)ethoxy]phenyl}-5-fluoro-2,4-pyrimidinediamine
53	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
54	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(3 <i>R</i> ,5 <i>S</i>)-3,5-dimethyl-1-piperidinyl]ethoxy}-4-methylphenyl)-2,4-pyrimidinediamine
55	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(3 <i>R</i> ,5 <i>S</i>)-3,5-dimethyl-1-piperidinyl]ethoxy}-4-methylphenyl)-5-fluoro-2,4-pyrimidinediamine
56	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(2 <i>R</i> ,6 <i>S</i>)-2,6-dimethyl-1-piperidinyl]ethoxy}phenyl)-2,4-pyrimidinediamine
57	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(2 <i>R</i> ,6 <i>S</i>)-2,6-dimethyl-1-piperidinyl]ethoxy}phenyl)-5-fluoro-2,4-pyrimidinediamine
58	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(3 <i>R</i> ,5 <i>R</i>)-3,5-dimethyl-1-piperidinyl]ethoxy}-4-methylphenyl)-2,4-pyrimidinediamine
59	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(4-methyl-1-

	piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
60	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -{3-[2-(4-methyl-1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
61	N^2 -{3-[2-(4-benzyl-1-piperidinyl)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
62	N^2 -{3-[2-(4-benzyl-1-piperidinyl)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro-2,4-pyrimidinediamine
63	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -{4-methoxy-3-[2-(4-morpholinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
64	5-bromo- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
65	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-5-methyl-2,4-pyrimidinediamine
66	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-5-fluoro-2,4-pyrimidinediamine
67	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -{3-[2-(4-morpholinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
68	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-chloro- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
69	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-chloro- N^2 -{3-[2-(4-morpholinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
70	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{4-chloro-3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
71	5-bromo- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(4-morpholinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
72	N^2 -{3-[2-(benzylamino)ethoxy]phenyl}- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro-2,4-pyrimidinediamine
73	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-methyl- N^2 -{3-[2-(4-morpholinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
74	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
75	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-5-fluoro-2,4-pyrimidinediamine
76	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(4-morpholinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
77	1-{2-[3-({4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-

	pyrimidinyl amino)phenoxy]ethyl}- <i>N,N</i> -diethyl-3-piperidinecarboxamide
78	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[2-(diethylamino)ethoxy]-4-methylphenyl}-2,4-pyrimidinediamine
79	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[2-(diethylamino)ethoxy]-4-methylphenyl}-5-fluoro-2,4-pyrimidinediamine
80	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[3-(diethylamino)propoxy]phenyl}-2,4-pyrimidinediamine
81	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[3-(diethylamino)propoxy]phenyl}-5-fluoro-2,4-pyrimidinediamine
82	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{4-methyl-3-[2-(4-morpholinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
83	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{4-methyl-3-[(1-methyl-2-piperidinyl)methoxy]phenyl}-2,4-pyrimidinediamine
84	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{4-methyl-3-[(1-methyl-2-piperidinyl)methoxy]phenyl}-2,4-pyrimidinediamine
85	<i>N</i> ² -{4-methyl-3-[(1-methyl-2-piperidinyl)methoxy]phenyl}- <i>N</i> ⁴ -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
86	<i>N</i> -[5-fluoro-2-({4-methyl-3-[(1-methyl-2-piperidinyl)methoxy]phenyl} amino)-4-pyrimidinyl]- <i>N</i> -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)amine
87	<i>N</i> ⁴ -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]- <i>N</i> ² -{4-methyl-3-[(1-methyl-2-piperidinyl)methoxy]phenyl}-2,4-pyrimidinediamine
88	<i>N</i> ⁴ -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]-5-fluoro- <i>N</i> ² -{4-methyl-3-[(1-methyl-2-piperidinyl)methoxy]phenyl}-2,4-pyrimidinediamine
89	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{3-[(1-methylhexahydro-3-pyridazinyl)methoxy]phenyl}-2,4-pyrimidinediamine
90	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{4-methoxy-3-[(1-methylhexahydro-3-pyridazinyl)methoxy]phenyl}-2,4-pyrimidinediamine
91	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{4-methoxy-3-[(1-methylhexahydro-3-pyridazinyl)methoxy]phenyl}-2,4-pyrimidinediamine

92	N^2 -{4-methoxy-3-[(1-methylhexahydro-3-pyridazinyl)methoxy]phenyl}- N^4 -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
93	5-fluoro- N^2 -{4-methoxy-3-[(1-methylhexahydro-3-pyridazinyl)methoxy]phenyl}- N^4 -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
94	N -[5-fluoro-2-({3-[(1-methylhexahydro-3-pyridazinyl)methoxy]phenyl} amino)-4-pyrimidinyl]- N -(3- <i>tert</i> -pentyl-1 <i>H</i> -pyrazol-5-yl)amine
95	N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]-5-fluoro- N^2 -{4-methoxy-3-[(1-methylhexahydro-3-pyridazinyl)methoxy]phenyl}-2,4-pyrimidinediamine
96	N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]-5-fluoro- N^2 -{3-[(1-methylhexahydro-3-pyridazinyl)methoxy]phenyl}-2,4-pyrimidinediamine
97	N^4 -[3-(1-ethyl-1-methylpropyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{4-methoxy-3-[(1-methylhexahydro-3-pyridazinyl)methoxy]phenyl}-2,4-pyrimidinediamine
98	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[(1-methylhexahydro-3-pyridazinyl)methoxy]phenyl}-2,4-pyrimidinediamine
99	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[(1-methyl-2-piperidinyl)methoxy]phenyl}-2,4-pyrimidinediamine
100	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -{3-[(1-methyl-2-piperidinyl)methoxy]phenyl}-2,4-pyrimidinediamine
101	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(4-methoxy-3-{[2-(1-piperidinyl)cyclohexyl]oxy}phenyl)-2,4-pyrimidinediamine
102	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -(4-methoxy-3-{[2-(1-piperidinyl)cyclohexyl]oxy}phenyl)-2,4-pyrimidinediamine
103	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -[3-[2-(diethylamino)ethoxy]-4-(4-methoxyphenoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine
104	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -[3-[2-(diethylamino)ethoxy]-4-(3,4-dimethylphenoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine
105	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -[3-[2-(diethylamino)ethoxy]-4-(3,4-dimethylphenoxy)phenyl]-2,4-pyrimidinediamine

106	N^2 -{3-[2-(3-azabicyclo[3.2.2]non-3-yl)ethoxy]-4-methylphenyl}- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro-2,4-pyrimidinediamine
107	N^2 -{3-[2-(3-azabicyclo[3.2.2]non-3-yl)ethoxy]-4-methylphenyl}- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
108	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(4-methoxy-3-{2-[(2-methoxy-1-methylethyl)amino]ethoxy}phenyl)-2,4-pyrimidinediamine
109	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(2-ethylbutyl)amino]ethoxy}-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine
110	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(cyclohexylmethyl)amino]ethoxy}phenyl)-2,4-pyrimidinediamine
111	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(1-methylbutyl)amino]ethoxy}phenyl)-2,4-pyrimidinediamine
112	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(4-methylcyclohexyl)amino]ethoxy}phenyl)-2,4-pyrimidinediamine
113	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(cyclopentylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
114	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -(4-methoxy-3-{2-[(2-methoxy-1-methylethyl)amino]ethoxy}phenyl)-2,4-pyrimidinediamine
115	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(2-ethylbutyl)amino]ethoxy}-4-methoxyphenyl)-2,4-pyrimidinediamine
116	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -{4-methoxy-3-[2-(neopentylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
117	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{4-methoxy-3-[2-(neopentylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
118	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -[4-methoxy-3-(2-{[2-(4-morpholinyl)ethyl]amino}ethoxy)phenyl]-2,4-pyrimidinediamine
119	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -[4-methoxy-3-(2-{[2-(4-morpholinyl)ethyl]amino}ethoxy)phenyl]-2,4-pyrimidinediamine
120	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{[2-(diethylamino)ethyl]amino}phenyl)-2,4-pyrimidinediamine
121	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{[2-

	(diethylamino)ethyl]amino} phenyl)-5-methyl-2,4-pyrimidinediamine
122	5-bromo- <i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(diethylamino)ethyl]amino} phenyl)-2,4-pyrimidinediamine
123	5-bromo- <i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(4-morpholinyl)ethyl]amino} phenyl)-2,4-pyrimidinediamine
124	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(4-morpholinyl)ethyl]amino} phenyl)-2,4-pyrimidinediamine
125	<i>N</i> ² -{3-[2-(diethylamino)ethoxy]phenyl}- <i>N</i> ⁴ -(3-phenyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
126	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-methyl- <i>N</i> ² -(3-{[2-(4-morpholinyl)ethyl]amino} phenyl)-2,4-pyrimidinediamine
127	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(diethylamino)ethyl]amino} phenyl)-5-fluoro-2,4-pyrimidinediamine
128	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-chloro- <i>N</i> ² -(3-{[2-(diethylamino)ethyl]amino} phenyl)-2,4-pyrimidinediamine
129	3-({2-[3-({4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl} amino)phenoxy]ethyl} amino)benzoic acid
130	3-({2-[3-({4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl} amino)phenoxy]ethyl} amino)benzoic acid
131	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(diethylamino)ethyl]sulfanyl} phenyl)-2,4-pyrimidinediamine
132	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(diethylamino)ethyl]sulfanyl} phenyl)-5-fluoro-2,4-pyrimidinediamine
133	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(diethylamino)ethyl]sulfonyl} phenyl)-2,4-pyrimidinediamine
134	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(diethylamino)ethyl]sulfonyl} phenyl)-5-fluoro-2,4-pyrimidinediamine
135	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{3-[2-(1-methyl-2-pyrrolidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
136	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[2-(diisopropylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
137	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[(1-methyl-4-azepanyl)oxy]phenyl}-2,4-pyrimidinediamine

138	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{3-[(1-methyl-4-azepanyl)oxy]phenyl}-2,4-pyrimidinediamine
139	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[2-(1-methyl-2-pyrrolidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
140	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[2-(1-pyrrolidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
141	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{3-[2-(1-pyrrolidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
142	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[2-(diisopropylamino)ethoxy]phenyl}-5-fluoro-2,4-pyrimidinediamine
143	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{2-[methyl(phenyl)amino]ethoxy}phenyl)-2,4-pyrimidinediamine
144	1-{2-[3-({4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl}amino)phenoxy]ethyl}-2-pyrrolidinone
145	1-{2-[3-({4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl}amino)phenoxy]ethyl}-2-pyrrolidinone
146	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[2-(1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
147	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{3-[2-(1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
148	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(diethylamino)ethoxy]methyl}phenyl)-2,4-pyrimidinediamine
149	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(diethylamino)ethoxy]methyl}phenyl)-5-fluoro-2,4-pyrimidinediamine
150	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(diisopropylamino)ethoxy]methyl}phenyl)-2,4-pyrimidinediamine
151	1-{2-[5-({4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl}amino)-2-methoxyphenoxy]ethyl}-2-pyrrolidinone
152	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(diisopropylamino)ethoxy]methyl}phenyl)-5-fluoro-2,4-pyrimidinediamine
153	1-{2-[5-({4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl}amino)-2-methylphenoxy]ethyl}-2-pyrrolidinone
154	1-{2-[5-({4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl}amino)-2-methylphenoxy]ethyl}-2-pyrrolidinone

155	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diisopropylamino)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
156	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diisopropylamino)ethoxy]-4-methoxyphenyl}-5-fluoro-2,4-pyrimidinediamine
157	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diisopropylamino)ethoxy]-4-methylphenyl}-2,4-pyrimidinediamine
158	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diisopropylamino)ethoxy]-4-methylphenyl}-5-fluoro-2,4-pyrimidinediamine
159	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{4-methyl-3-[2-(1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
160	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -{4-methyl-3-[2-(1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
161	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{4-methoxy-3-[2-(1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
162	1-(2-{[3-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl)amino]benzyl}oxy)ethyl)-2-pyrrolidinone
163	1-(2-{[3-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl)amino]benzyl}oxy)ethyl)-2-pyrrolidinone
164	1-(2-{[5-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl)amino]-2-methoxybenzyl}oxy)ethyl)-2-pyrrolidinone
165	1-(2-{[5-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl)amino]-2-methoxybenzyl}oxy)ethyl)-2-pyrrolidinone
166	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{[2-(diethylamino)ethoxy]methyl}-4-methoxyphenyl)-2,4-pyrimidinediamine
167	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{[2-(diethylamino)ethoxy]methyl}-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine
168	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{[2-(diisopropylamino)ethoxy]methyl}-4-methoxyphenyl)-2,4-pyrimidinediamine
169	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{[2-(diisopropylamino)ethoxy]methyl}-4-methoxyphenyl)-5-fluoro-

	2,4-pyrimidinediamine
170	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{4-methyl-3-[2-(1-pyrrolidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
171	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -[3-(4-morpholinylmethyl)phenyl]-2,4-pyrimidinediamine
172	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -[3-(4-morpholinylmethyl)phenyl]-2,4-pyrimidinediamine
173	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -[4-methoxy-3-(4-morpholinylmethyl)phenyl]-2,4-pyrimidinediamine
174	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -[4-methoxy-3-(4-morpholinylmethyl)phenyl]-2,4-pyrimidinediamine
175	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{3-[(4-methyl-1-piperazinyl)methyl]phenyl}-2,4-pyrimidinediamine
176	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{3-[(4-methyl-1-piperazinyl)methyl]phenyl}-2,4-pyrimidinediamine
177	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{4-methoxy-3-[(4-methyl-1-piperazinyl)methyl]phenyl}-2,4-pyrimidinediamine
178	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{4-methoxy-3-[(4-methyl-1-piperazinyl)methyl]phenyl}-2,4-pyrimidinediamine
179	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{4-methoxy-3-[2-(1-pyrrolidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
180	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -{4-methoxy-3-[2-(1-piperidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
181	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -{4-methoxy-3-[2-(1-pyrrolidinyl)ethoxy]phenyl}-2,4-pyrimidinediamine
183	<i>N</i> -[3-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl)amino]phenyl]-2-(1-piperidinyl)acetamide
184	<i>N</i> -[3-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl)amino]phenyl]-2-(1-piperidinyl)acetamide
185	<i>N</i> ¹ -[3-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl)amino]phenyl]- <i>N</i> ² , <i>N</i> ² -diethylglycinamide
186	<i>N</i> ¹ -[3-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl)amino]phenyl]- <i>N</i> ² , <i>N</i> ² -diethylglycinamide
187	<i>N</i> -[3-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl)amino]phenyl]-2-(1-pyrrolidinyl)acetamide
188	<i>N</i> -[3-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl)amino]phenyl]-2-(1-pyrrolidinyl)acetamide

182	<i>N</i> -[3-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl)amino)phenyl]-2-(4-morpholinyl)acetamide
189	<i>N</i> -[3-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl)amino)phenyl]-2-(4-morpholinyl)acetamide
190	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{[2-(1-piperidinyl)ethyl]amino}phenyl)-2,4-pyrimidinediamine
191	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- <i>N</i> ² -(3-{[2-(1-piperidinyl)ethyl]amino}phenyl)-2,4-pyrimidinediamine
192	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-[3-(diethylamino)propyl]-4-methoxyphenyl)-2,4-pyrimidinediamine
193	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-[3-(diethylamino)propyl]-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine
195	1-{2-[5-(4-[(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)amino]-2-pyrimidinyl)amino]-2-methoxyphenoxy}ethyl}-2-pyrrolidinone
196	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(4-methoxy-3-[2-(4-morpholinyl)ethoxy]phenyl)-2,4-pyrimidinediamine
194	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-[3-(diethylamino)-1-propynyl]phenyl)-2,4-pyrimidinediamine
197	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-[2-(diethylamino)ethoxy]-4-(1-pyrrolidinyl)phenyl]-5-fluoro-2,4-pyrimidinediamine
198	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-[2-(diethylamino)ethoxy]-4-(1-pyrrolidinyl)phenyl)-2,4-pyrimidinediamine
199	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{2-[(2 <i>R</i> ,6 <i>R</i>)-2,6-dimethyl-4-morpholinyl]ethoxy}-4-methylphenyl)-2,4-pyrimidinediamine
200	<i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- <i>N</i> ² -(3-{2-[(2 <i>R</i> ,6 <i>R</i>)-2,6-dimethyl-4-morpholinyl]ethoxy}-4-methylphenyl)-5-fluoro-2,4-pyrimidinediamine
201	<i>N</i> ² -(3-{2-[butyl(ethyl)amino]ethoxy}-4-methylphenyl)- <i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
202	<i>N</i> ² -(3-{2-[benzyl(ethyl)amino]ethoxy}-4-methylphenyl)- <i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
203	<i>N</i> ² -(3-{2-[butyl(ethyl)amino]ethoxy}-4-methylphenyl)- <i>N</i> ⁴ -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro-2,4-pyrimidinediamine

204	N^2 -(3-{2-[benzyl(ethyl)amino]ethoxy}-4-methylphenyl)- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro-2,4-pyrimidinediamine
205	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(2 <i>R</i> ,6 <i>S</i>)-2,6-dimethyl-4-morpholinyl]ethoxy}-4-methylphenyl)-2,4-pyrimidinediamine
206	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(3-{2-[(2 <i>R</i> ,6 <i>S</i>)-2,6-dimethyl-4-morpholinyl]ethoxy}-4-methylphenyl)-5-fluoro-2,4-pyrimidinediamine
207	N^2 -(3-{2-(3-azabicyclo[3.2.2]non-3-yl)ethoxy}-4-methylphenyl)-5-fluoro- N^4 -[3-(1-methylcyclopropyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
208	N^2 -(3-{2-[butyl(ethyl)amino]ethoxy}-4-methylphenyl)-5-fluoro- N^4 -[3-(1-methylcyclopropyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
209	N^2 -(3-{2-[benzyl(ethyl)amino]ethoxy}-4-methylphenyl)-5-fluoro- N^4 -[3-(1-methylcyclopropyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
210	N^2 -(3-{2-[(2 <i>R</i> ,6 <i>R</i>)-2,6-dimethyl-4-morpholinyl]ethoxy}-4-methylphenyl)-5-fluoro- N^4 -[3-(1-methylcyclopropyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
211	N^2 -(3-{2-[(2 <i>R</i> ,6 <i>S</i>)-2,6-dimethyl-4-morpholinyl]ethoxy}-4-methylphenyl)-5-fluoro- N^4 -[3-(1-methylcyclopropyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
212	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(5-[2-(diethylamino)ethoxy]-2-methylphenyl)-5-fluoro-2,4-pyrimidinediamine
213	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(4-[2-(diethylamino)ethoxy]phenyl)-5-methyl-2,4-pyrimidinediamine
214	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(5-[2-(diethylamino)ethoxy]-2-methylphenyl)-2,4-pyrimidinediamine
215	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(8-[2-(diethylamino)ethoxy]-6-quinolinyl)-2,4-pyrimidinediamine
216	5-bromo- N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(4-[2-(diethylamino)ethoxy]phenyl)-2,4-pyrimidinediamine
217	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -(4-(4-morpholinylmethyl)phenyl)-2,4-pyrimidinediamine
218	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)-5-fluoro- N^2 -(4-(4-

	morpholinylmethyl)phenyl]-2,4-pyrimidinediamine
219	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{4-[4-(1 <i>H</i> -pyrrol-1-yl)-1-piperidinyl]phenyl}-2,4-pyrimidinediamine
220	N^4 -(3- <i>tert</i> -butyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -[4-(4-methyl-1-piperazinyl)phenyl]-2,4-pyrimidinediamine
221	N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -[3-(1-methylcyclopropyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
222	N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^4 -[3-(trifluoromethyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
223	N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -[3-(trifluoromethyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
224	N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^4 -(3-neopentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
225	N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -(3-neopentyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
226	N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^4 -(1,3-dimethyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
227	N^4 -(3-cyclopropyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
228	N^4 -(3-cyclopropyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
229	N^4 -(3-cyclopentyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
230	N^4 -(3-cyclopentyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
231	N^4 -[3-(1-adamantyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
232	N^4 -[3-(1-adamantyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
233	N^4 -[3-(2- <i>tert</i> -butyl-5-methyl-3-furyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
234	N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^4 -[3-(2-furyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
235	5-[[2-({3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}amino)-4-pyrimidinyl]amino]- <i>N,N</i> -diethyl-1 <i>H</i> -pyrazole-3-carboxamide
236	3-(4-chlorophenyl)-5-[[2-({3-[2-(diethylamino)ethoxy]phenyl}amino)-4-pyrimidinyl]amino]-1 <i>H</i> -pyrazole-4-carbonitrile

237	N^4 -(3-cyclopropyl-1-methyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
238	N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -(1-ethyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
239	N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -(3-methyl-1-phenyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
240	N^4 -(3- <i>tert</i> -butyl-1-methyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
241	N^4 -[3-(4-chlorophenyl)-1-methyl-1 <i>H</i> -pyrazol-5-yl]- N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
242	N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -(3-phenyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
243	N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -(4-fluoro-2 <i>H</i> -indazol-3-yl)-2,4-pyrimidinediamine
244	N^4 -(3-cyclopropyl-1-methyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
245	N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^4 -(1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
246	N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^4 -(3-methyl-1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
247	N^4 -[3-(4-chlorophenyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
248	N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -(1 <i>H</i> -pyrazol-5-yl)-2,4-pyrimidinediamine
249	ethyl 5-{[2-({3-[2-(diethylamino)ethoxy]phenyl}amino)-4-pyrimidinyl]amino}-1 <i>H</i> -pyrazole-4-carboxylate
250	N^4 -[3-(4-chlorophenyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
251	N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^4 -(4-fluoro-2 <i>H</i> -indazol-3-yl)-2,4-pyrimidinediamine
252	N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^4 -[3-(2-thienyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine
253	N^4 -[3-(4-chlorophenyl)-1-methyl-1 <i>H</i> -pyrazol-5-yl]- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
254	N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^4 -[3-(4-methylphenyl)-1 <i>H</i> -pyrazol-5-yl]-2,4-pyrimidinediamine

255	N^4 -[3-(5- <i>tert</i> -butyl-2-methyl-3-furyl)-1 <i>H</i> -pyrazol-5-yl]- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
256	N^4 -(3-cyclohexyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
257	N^4 -(3- <i>tert</i> -butyl-1-methyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine
258	N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -{3-[1-methyl-1-(1 <i>H</i> -1,2,4-triazol-1-yl)ethyl]-1 <i>H</i> -pyrazol-5-yl}-2,4-pyrimidinediamine
259	N^4 -(3- <i>tert</i> -butyl-1-methyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^2 , N^4 -dimethyl-2,4-pyrimidinediamine
260	N^4 -(3- <i>tert</i> -butyl-1-methyl-1 <i>H</i> -pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^2 -methyl-2,4-pyrimidinediamine

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the
5 racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of a compound of the present invention is
10 desired, it may be prepared by asymmetric synthesis, or by derivatization with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group such as amino, or an acidic functional group such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by
15 resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Contemplated equivalents of the compounds described above include compounds which otherwise correspond thereto, and which have the same general properties thereof (e.g., functioning as src kinase inhibitors), wherein one or more simple variations of
20 substituents are made which do not adversely affect the efficacy of the compound in

inhibiting src kinases.

In general, the compounds of the present invention may be prepared by the methods known to those skilled in the art as illustrated in the general reaction schemes described below, or by modifications thereof, using readily available starting materials, reagents and
5 conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

Methods of use of the compounds of the invention

The compounds of the invention, including substituted pyrimidine compounds, salts,
10 prodrugs, and compositions thereof, can be used for treating a disease or condition (generally referred to herein as “disease”) associated with a kinase, such as a disease associated with an abnormal activity or level of a kinase. In a preferred embodiment, the kinase is a tyrosine kinase, such as a src tyrosine kinase. Generally, the compounds of the invention can be used for treating diseases that are associated with a component of the signal transduction pathway
15 in which a kinase is involved. For example, it is expected that a cell proliferative disease resulting from over-expression of a signal transduction molecule or cell surface receptor that is in the same signal transduction pathway as that in which a kinase which can be inhibited by a compound of the invention is present, can also be treated with the compounds of the invention. At least for this reason, the compounds of the invention are expected to be
20 effective against a broad range of target cells, and not only target cells having an abnormal activity or level of a kinase. The terms “target cell” refers to a cell towards which a compound is targeted. Furthermore, at least some of the compounds of the invention may also be effective against cells which proliferate and/or differentiate normally, i.e., wild-type cells. For example, certain compounds could be used to arrest cell proliferation, even if the
25 cell proliferation is not abnormal.

In a preferred embodiment, the compounds of the invention are useful for treating a disease associated with a src kinase. Src kinases are involved in various cellular functions, including cell proliferation and transformation; cell adhesion, migration and chemotaxis; intracellular trafficking; and cell survival. Accordingly, diseases that can be treated
30 according to the invention include those which are dysfunctional in any of these cellular functions. Exemplary diseases are provided below.

In one embodiment, a therapeutic method comprises administering to a subject having a disease associated with a kinase, a pharmaceutically effective amount of a compound of the invention, such that the disease is treated. The subject is preferably a mammal, e.g., a human, non-human primate, bovine, ovine, porcine, feline, canine, mouse or rat. The compounds can be administered via various routes depending on the disease to be treated. Methods of administration are further described herein. Non-mammalian cells, which share essentially the same signal transduction pathways as those in mammalian cells, e.g., yeast cells, can also be target cells of the invention.

Compounds of the invention may specifically inhibit the activity of a single kinase, e.g., src kinase, or they may inhibit the activity of more than one kinase or more than one type of kinase. Accordingly, a compound of the invention could be used for treating one or more diseases associated with one or more kinases.

The efficacy of the compounds of the invention against a broad range of target cells allows for broad applications for these compounds. The following are exemplary therapeutic applications for the compounds of the invention. These exemplary therapeutic applications focus first on diseases associated with src tyrosine kinase and then describe other diseases that may also be treated with the compounds of the invention.

Src tyrosine kinase has specifically been implicated in the development, growth, progression, and metastasis of a number of human cancers such as colon, breast, pancreas and brain (*see, e.g.,* Irby and Yeatman (2000) *Oncogene* 19:5636), and these cancers are expected to be treatable with the compounds of the invention. For example, a src kinase activity from 4-20 fold higher than normal has been found in mammary carcinomas (Irby and Yeatman, *supra*; Egan *et al.* (1999) *Oncogene* 18:1227 and Verbeek *et al.* (1996) *J. Pathol.* 180:383).

c-src has also frequently been implicated in the initiation and progression of human colon cancer and in resultant metastases (*see, e.g.,* Cartwright *et al.* (1994) *J. Clin. Invest.* 93:509; Talamonti *et al.* (1991) *J. Clin. Invest.* 91:53; and Termuhlen *et al.* (1993) *J. Surg. Res.* 54). Src is increased 5-8 fold in the majority of colon tumors. Elevated src activity is also present in pre-cancerous colon lesions, e.g., adenomatous polyps (Pena *et al.* (1995) *Gastroenterol.* 108:117).

Other cancers that can be treated include pancreatic cancer (Flossmann-Kast *et al.* (1998) *Cancer Res.* 8:3551); and Visser *et al.* (1996) *Lab. Invest.* 74:2), lung cancer

(Mazurenko *et al.* (1992) *Eur. J. Cancer* 28:372), neural cancer (Bjelfman *et al.* (1990) *Cancer Res.* 50:6908); ovarian cancer (Wiener *et al.* (1999) *Clin. Cancer Res.* 5:2164); esophageal adenocarcinomas and Barrett's (Kumble *et al.* (1997) *Gastroenterology* 112:348); gastric cancers (Takeshima *et al.* (1991) *Jpn. J. Cancer Res.* 82:1428); melanomas
5 (Bjorge *et al.* (1996) *Biochem. Cell Biol.* 74:477) and Kaposi's sarcoma (Munshi *et al.* (2000) *J. Immunol.* 164:1169). Src probably also contributes to tumor growth in synergy with receptor tyrosine kinases, such as c-met and those of the ErbB family (Biscardi *et al.* (1999) *Adv. Cancer Res.* 76: 6). Accordingly, all of the above are exemplary cancers that can be treated with the compounds of the invention.

10 The compounds of the invention can also be used to treat diseases associated with defects in cell adhesion and motility, such as angiogenesis, inflammation and bone resorption. Src has been shown to play a role in signal transduction via cell-adhesion receptors (integrins). Src dependent cell migration is important for the function of many cell types, e.g., the motility of osteoclasts and metastasizing cells (Chellaiah *et al.* (2000) *J. Biol.*
15 *Chem.* 275:11993 and Susa and Teri (2000) *Drug News Perspect.* 13:169). Src dependent cell migration may also be important for the recruitment of vascular smooth muscle cell precursors in response to PDGF produced by endothelial cells during blood vessel formation (Hirschi *et al.* (1998) *J. Cell. Biol.* 141:805).

 Src kinase is also involved in endocytosis, e.g., transcytosis, such as that which
20 occurs in osteoclasts (Nesbitt and Horton (1997) *Science* 276:266). Src assists endocytosis of certain growth factor receptors, e.g., EGF receptors (Wilde *et al.* (1999) *Cell* 96:677). Blood vessel hyperpermeability induced by vascular endothelial growth factor (VEGF) is also dependent on src (Eliceiri *et al.* (1999) *Mol. Cell* 4:915). Src has been shown to also be involved in cell survival (reviewed in Susa *et al.* (2000) *Trends in Pharmacol. Sci.* 21:489).
25 Accordingly, diseases related to any of these exemplary src biological activities can be treated with the compounds of the invention.

 A preferred use for the compounds of the invention is for the treatment of osteoporosis, which involves bone resorption. Osteoporosis is a widespread disease of low bone mass that particularly affects post-menopausal women (*see, e.g.,* Gowen *et al.* (2000)
30 *Emerging Drugs* 5:1). The role of src in bone metabolism was first demonstrated in src-deficient mice and has been confirmed using small molecular weight inhibitors in animal models of osteoporosis. Src-deficient mice have defective bone resorption, resulting in

excessive bone mass and osteopetrosis (*see, e.g.,* Thomas and Brugge (1997) *Annu. Rev. Cell. Dev. Biol.*, 13: 513). The role of src in bone resorption is well recognized. A src inhibitor has been shown to reduce bone resorption in an animal model of osteoporosis (Missbach *et al.* (1992) *Bone* 24:437). The disorder is believed to be caused by dysfunctions
5 in osteoclasts and osteoblasts, as well as in osteoclast survival and osteoclast formation (reviewed in Susa *et al., supra*).

Other diseases that may also be treated according to the invention include other types of malignancies, e.g., cancers of the brain, genitourinary tract, prostate, skin, lymphatic system, rectum, stomach, larynx, ovary, bladder, and liver. More particularly, such cancers
10 include histiocytic lymphoma, lung adenocarcinoma, pancreatic carcinoma, colo-rectal carcinoma, bladder cancers, head and neck cancers, acute and chronic leukemias, melanomas, neurological tumor, myeloid leukemias (for example, acute myelogenous leukemia), sarcomas, thyroid follicular cancer, and myelodysplastic syndrome.

The compounds of the invention can also be used for treating disease associated with
15 abnormal activity and/or expression of members of a growth factor family or receptors thereof. For example, compounds of the invention are expected to be effective against diseases associated with a defect in a growth factor or receptor of the EGF receptor family, such as Neu-erb2-related genes. The compounds of the invention are believed to be effective against the following diseases. For example, amplification and/or over-expression of human
20 erbB2 gene, has been shown to correlate with a poor prognosis in breast and ovarian cancers, in particular, carcinomas (*see, e.g.,* Slamon *et al.*, *Science* 235:177-82 (1987); Slamon *et al.*, *Science* 244:707-12 (1989)). Overexpression of erbB2 has also been correlated with other carcinomas including carcinomas of the stomach, endometrium, salivary gland, lung, kidney, colon and bladder. ErbB1 has been causally implicated in human malignancy, e.g.,
25 aggressive carcinomas of the breast, bladder, lung, and stomach. ErbB gene amplification or overexpression, or a combination of both, has also been demonstrated in squamous cell carcinomas and glioblastomas (Libermann, T. A., Nusbaum, H. R., Razon, N., Kris, R., Lax, I., Soreq, H., Whittle, N., Waterfield, M.D., Ullrich, A. & Schlessinger, J., 1985, *Nature* 313:144-147). Accordingly, the compounds of the invention are believed to be useful for
30 treating these malignancies. ErbB3 has been found to be overexpressed in breast (Lemoine *et al.*, *Br. J. Cancer* 66:1116-21 (1992)), gastrointestinal (Poller *et al.*, *J. Pathol.* 168:275-80 (1992); Rajkumar *et al.*, *J. Pathol.* 170:271-78 (1993); Sanidas *et al.*, *Int. J. Cancer* 54:935-

40 (1993)), and pancreatic cancers (Lemoine *et al.*, J. Pathol. 168:269-73 (1992), and Friess *et al.*, Clinical Cancer Research 1:1413-20 (1995)). Plowman *et al.* found that Increased erbB4 expression have been found to closely correlate with certain carcinomas of epithelial origin, including breast adenocarcinomas (Plowman *et al.*, PNAS 90:1746-50 (1993) and
5 Plowman *et al.*, Nature 366:473-75 (1993)).

The hyper-proliferative disorders that can be treated by the disclosed substituted pyrimidine compounds, salts, prodrugs and compositions thereof include, but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their
10 distant metastases. Those disorders also include, but are not limited to lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell
15 and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophthalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

20 Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer.

Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal,
25 esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma
30 (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's

sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell
5 lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma. Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

10 These disorders have been well characterized in man, but also exist with a similar etiology in other mammals, and can be treated by pharmaceutical compositions of the present invention.

Other types of proliferative disorders that can be treated according to the invention include non malignant cell proliferative disorders, such as those associated with an abnormal
15 production of, or response to a growth factor, e.g., platelet derived growth factor (PDGF), fibroblast derived growth factor (FGF), epidermal derived growth factor (EGF) and vascular endothelial growth factor (VEGF). Exemplary diseases include restenosis, glomerulonephritis, neurofibromatosis, glaucoma, psoriasis, rheumatoid arthritis, inflammatory bowel disease, and chemotherapy-induced alopecia and mucositis.

20 Restenosis following coronary angioplasty is one major unsolved problem of interventional cardiology. Of the nearly 400,000 angioplasties currently performed in the United States each year, 25-34% fail within the first five years, of which most occur during the first year, due to restenosis (Geschwind H.J. (1995) Interv. Cardiol. 8:756 and The Merck Manual of Diagnosis and Therapy, 16th Ed. (1992) Merck Res. Lab., p. 406. The process of
25 restenosis involves the reocclusion of an atherosclerotic artery which in many cases is due to the proliferation of smooth muscle cells which is mediated by growth factors such as PDGF and FGF. In animal models of restenosis, antibodies which block the activation of PDGF or FGF receptor tyrosine kinase activity prevent smooth muscle cell proliferation and the formation of neointima. These studies indicate that tyrosine kinase inhibitors that block
30 PDGF or FGF receptor function could have utility in treating human restenosis.

In experimental models of glomerulonephritis, a 20-fold increase in PDGFR expression is associated with mesangial cell proliferation. Neutralization of PDGF which

prevents the activation of its tyrosine kinase receptor limits the amount of renal degeneration which normally occurs. These studies demonstrate that a tyrosine kinase inhibitor which blocks PDGFR could have potential for the treatment of human glomerulonephritis. Johnson *et al.* (1992) J. Exp. Med. 175:1413.

5 In another embodiment, the compounds of the invention are used for treating inflammatory diseases, e.g., rheumatoid arthritis (R.A.). Synovial tissues of RA patients express high levels of FGF and PDGF compared with synovial tissues of osteoarthritis patients, a non invasive joint disease (Sano *et al.*, J. Cell. Biol. 110:1417-1426, 1990). These data are consistent with the theory that PDGF and FGF play a role in generating an invasive
10 tumor-like behavior in arthritic joints of RA synovial connective tissues (Sano *et al.*, J. Clin. Invest. 91:553-565 1993).

It is further expected that the compounds of the invention are useful for treating smooth muscle cell hyper-proliferation, at least in part since PDGF is considered to be a principal growth-regulatory molecule responsible for smooth muscle cell proliferation. One
15 smooth muscle disorder is atherosclerosis, which is a disease characterized by focal thickening of the inner portion of the artery wall, predisposing an individual to myocardial infarction (heart attack), cerebral infarction (stroke), hypertension (high blood pressure) and gangrene of the extremities. In addition to consisting primarily of proliferated smooth muscle cells, lesions of atherosclerosis are surrounded by large amounts of lipid-laden macrophages,
20 varying numbers of lymphocytes and large amounts of connective tissue. PDGF has been found in numerous cells in such lesions, and it is believed that PDGF plays a critical role in the atherosclerosis disease process. Other smooth muscle diseases include diabetic vascular pathologies.

Both FGF and VEGF are potent angiogenic factors that induce formation of new
25 capillary blood vessels. Accordingly, the compounds of the invention may be useful in inhibiting vascularization, e.g., in tumors.

In addition, the instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis C or delta and related viruses (Glenn *et al.* Science, 256:1331-1333 (1992)). Numerous viruses also induce non cancerous cell
30 proliferation. Examples include papilloma viruses (HPV), which create skin lesions. Such viral infections may also be treatable with the compositions of the invention.

The compounds of the invention can also be used for treatment of hyperproliferative cutaneous diseases, e.g., keratosis and psoriasis.

Also within the scope of the invention are methods for inhibiting growth of non-mammalian cells, which have similar signal transduction pathways as those in mammalian cells. Exemplary cells include yeast cells. Accordingly, the compounds of the invention can be used as anti-fungal agents to treat fungal infections on animals, e.g., humans. The compounds can also be used for stopping fungus growth on objects, e.g., mold or mildew growth on shower curtains.

A person of skill in the art would understand, based on the instant description, that other diseases can also be treated according to the invention.

Description of the Pharmaceutical Compositions and Methods of Administration of the Compounds of the Invention

Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds are also within the scope of the invention.

Salts, especially pharmaceutically acceptable salts, of the compounds of the invention such as, for example, organic or inorganic acid addition salts, are also provided by the invention. Suitable inorganic acids include but are not limited to halogen acids (such as hydrochloric acid), sulfuric acid, or phosphoric acid. Suitable organic acids include but are not limited to carboxylic, phosphonic, sulfonic, or sulfamic acids, with examples including acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2- or 3-hydroxybutyric acid, γ -aminobutyric acid (GABA), gluconic acid, glucosemonocarboxylic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azeiaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids (such as glutamic acid, aspartic acid, N-methylglycine, acetylaminoacetic acid, N-acetylasparagine or N-acetylcysteine), pyruvic acid, acetoacetic acid, phosphoserine, and 2- or 3-glycerophosphoric acid.

Formation of prodrugs is well known in the art in order to enhance the properties of the parent compound; such properties include solubility, absorption, biostability and release time (see "*Pharmaceutical Dosage Form and Drug Delivery Systems*" (Sixth Edition), edited by Ansel *et al.*, publ. by Williams & Wilkins, pgs. 27-29, (1995)). Commonly used prodrugs

of the disclosed 2,4-diamino-pyrimidine compounds can be designed to take advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention. Major drug biotransformation reactions include N-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff *et al.*, publ. by McGraw-Hill, pages 11-13, (1996)).

The invention also includes pharmaceutical compositions comprising one or more of the compounds of the invention, or their salts or prodrugs forms thereof, with a pharmaceutically acceptable ingredient.

The pharmaceutical compositions can be prepared so that they may be administered orally, dermally, parenterally, nasally, ophthalmically, otically, sublingually, rectally or vaginally. Dermal administration includes topical application or transdermal administration. Parenteral administration includes intravenous, intraarticular, intramuscular, and subcutaneous injections, as well as use of infusion techniques. One or more compounds of the invention may be present in association with one or more non-toxic pharmaceutically acceptable ingredients and optionally, other active anti-proliferative agents, to form the pharmaceutical composition. These compositions can be prepared by applying known techniques in the art such as those taught in *Remington's Pharmaceutical Sciences* (Fourteenth Edition), Managing Editor, John E. Hoover, Mack Publishing Co., (1970) or *Pharmaceutical Dosage Form and Drug Delivery Systems* (Sixth Edition), edited by Ansel *et al.*, publ. by Williams & Wilkins, (1995).

Commonly used pharmaceutical ingredients which can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents, examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid;

alkalinizing agents, examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, triethylamine;

adsorbents, examples include but are not limited to powdered cellulose and activated charcoal;

aerosol propellants, examples include but are not limited to carbon dioxide, CCl₂F₂, F₂ClC-

CClF₂ and CClF₃;

air displacement agents, examples include but are not limited to nitrogen and argon;

antifungal preservatives, examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate;

5 **antimicrobial preservatives**, examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal;

antioxidants, examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid,
10 monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite;

binding materials, examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers;

buffering agents, examples include but are not limited to potassium metaphosphate,
15 potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate;

carrying agents, examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection;

20 **chelating agents**, examples include but are not limited to edetate disodium and edetic acid;

colorants, examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red;

clarifying agents, examples include but are not limited to bentonite;

25 **emulsifying agents**, examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate;

encapsulating agents, examples include but are not limited to gelatin and cellulose acetate phthalate;

flavorants, examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol,
30 orange oil, peppermint oil and vanillin;

humectants, examples include but are not limited to glycerin, propylene glycol and sorbitol;

levigating agents, examples include but are not limited to mineral oil and glycerin;

oils, examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil;

ointment bases, examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment;

penetration enhancers (transdermal delivery), examples include but are not limited to monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas;

plasticizers, examples include but are not limited to diethyl phthalate and glycerin;

solvents, examples include but are not limited to alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation;

stiffening agents, examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax;

suppository bases, examples include but are not limited to cocoa butter and polyethylene glycols (mixtures);

surfactants, examples include but are not limited to benzalkonium chloride, nonoxynol 10, octoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate;

suspending agents, examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum;

sweetening agents, examples include but are not limited to aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose;

tablet anti-adherents, examples include but are not limited to magnesium stearate and talc;

tablet binders, examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch;

tablet and capsule diluents, examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch;

tablet coating agents, examples include but are not limited to liquid glucose, hydroxyethyl

cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac;

tablet direct compression excipients, examples include but are not limited to dibasic calcium phosphate;

5 **tablet disintegrants**, examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch;

tablet glidants, examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate;

tablet/capsule opaquants, examples include but are not limited to titanium dioxide;

tablet polishing agents, examples include but are not limited to carnuba wax and white wax;

thickening agents, examples include but are not limited to beeswax, cetyl alcohol and paraffin;

tonicity agents, examples include but are not limited to dextrose and sodium chloride;

viscosity increasing agents, examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth; and

20 **wetting agents**, examples include but are not limited to heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate.

Depending on the route of administration, the compositions can take the form of aerosols, capsules, creams, elixirs, emulsions, foams, gels, granules, inhalants, lotions, magmas, ointments, peroral solids, powders, sprays, syrups, suppositories, suspensions, tablets and tinctures.

The therapeutic methods of the invention generally comprise administering to a subject in need thereof, a pharmaceutically effective amount of a compound. The compounds of the invention can be administered in a amount effective to inhibit the activity of a kinase, e.g., a tyrosine kinase, such as src kinase. The compounds of the invention can also be administered in a "growth inhibitory amount," i.e., an amount of the compound which is pharmaceutically effective to inhibit or decrease proliferation of target cells. The

compounds can also be administered in a "differentiation modulating amount", e.g., "differentiation-inducing amount" or "differentiation-inhibiting amount," which is an amount of the compound which is pharmaceutically effective to modulate differentiation of target cells. The compounds of this invention may be administered to mammals, preferably
5 humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

10 Toxicity and therapeutic efficacy of the compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compounds which
15 exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such reagents to the site of affected tissue in order to minimize potential damage to normal cells and, thereby, reduce side effects.

Data obtained from cell culture assays and animal studies can be used in formulating
20 a range of dosage for use in humans. The dosage of such reagents lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any reagent used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may
25 be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Based on these assays, it is possible to derive an appropriate dosage for administration to subjects by combining IC₅₀ data with appropriate pharmacokinetic evaluation.

30 Pharmaceutical compositions containing a compound of the invention may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or

elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically
5 elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn
10 starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste
15 masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is
20 mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-
25 cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with
30 partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous

suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the compound of the invention in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

Pharmaceutical compositions may be in the form of sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

Sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the compound of the invention is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a
5 microemulsion.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous
10 intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUSTM model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or
15 wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or
20 diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of the invention may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at
25 the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing
30 the compound of the invention can be employed. For purposes of this application, topical application shall include mouth washes and gargles.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will preferably be continuous rather than intermittent throughout the dosage regimen.

The compounds of the invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. The compounds may be administered simultaneously or sequentially. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of osteoporosis, inflammation, neurofibromatosis, restinosis, and viral infections. The instant compounds may also be useful in combination with inhibitors of other components of signaling pathways of cell surface growth factor receptors.

Drugs can be co-administered to a subject being treated with a compound of the invention include antineoplastic agents selected from vinca alkaloids, epipodophyllotoxins, anthracycline antibiotics, actinomycin D, plicamycin, puromycin, gramicidin D, taxol, colchicine, cytochalasin B, emetine, maytansine, or amsacrine. Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, N.J. 07645-1742, USA).

Optional anti-proliferative agents that can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the Merck Index, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine,

raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff *et al.*, publ. by McGraw-Hill, pages 1225-1287, (1996),
5 such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine
10 phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone, irinotecan,
15 raloxifen and topotecan.

For all regimens of use disclosed herein for the invention, the daily oral dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and
20 parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal
25 concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when
30 administering therapeutics. It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, but not limited to the activity of the specific compound employed, the age of the patient, the body weight of the

patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy. It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of formulae (I) or (II) or a pharmaceutically acceptable salt thereof
5 given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

Radiation therapy, including x-rays or gamma rays which are delivered from either an externally applied beam or by implantation of tiny radioactive sources, may also be used in
10 combination with a compound of the invention to treat a disease, e.g., cancer.

When a composition according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

15

Kits of the invention

In one embodiment, compounds of the invention and/or materials and reagents required for administering the compounds of the invention may be assembled together in a kit. When the components of the kit are provided in one or more liquid solutions, the liquid
20 solution preferably is an aqueous solution, with a sterile aqueous solution being particularly preferred.

The kit may further comprise one or more other drugs, e.g., chemo- or radiotherapeutic agent. These normally will be a separate formulation, but may be formulated into a single pharmaceutically acceptable composition. The container means may itself be
25 geared for administration, such as an inhalant, syringe, pipette, eye dropper, or other such like apparatus, from which the formulation may be applied to an infected area of the body, such as the lungs, or injected into an animal, or even applied to and mixed with the other components of the kit.

The compositions of these kits also may be provided in dried or lyophilized forms.
30 When reagents or components are provided as a dried form, reconstitution generally is by the addition of a suitable solvent. It is envisioned that the solvent also may be provided in another container means. The kits of the invention may also include an instruction sheet

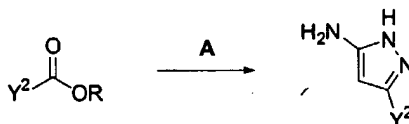
defining administration of the agent and, e.g., explaining how the agent will decrease proliferation of cells.

The kits of the present invention also will typically include a means for containing the vials in close confinement for commercial sale such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained. Irrespective of the number or type of containers, the kits of the invention also may comprise, or be packaged with a separate instrument for assisting with the injection/administration or placement of the ultimate complex composition within the body of an animal. Such an instrument may be an inhalant, syringe, pipette, forceps, measured spoon, eye dropper or any such medically approved delivery vehicle. Other instrumentation includes devices that permit the reading or monitoring of reactions.

The present invention is further illustrated by the following examples which should not be construed as limiting in any way. The contents of all cited references (including literature references, issued patents, published patent applications as cited throughout this application) are hereby expressly incorporated by reference.

Examples 1-260

General Method A. Preparation of 5-amino-3-substituted pyrazoles



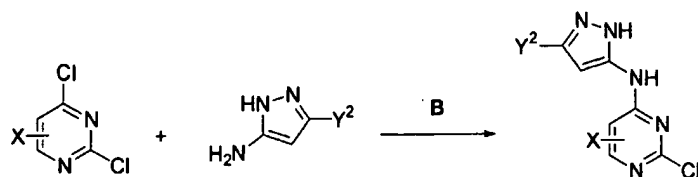
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To a mixture of NaH (2.1 equiv) and THF (0.15 M) is added CH_3CN (2.1 equiv) and the required ester (1 equiv). The suspension is stirred at 65 °C for 16 h. The reaction is then quenched with an alcohol such as EtOH at 0 °C. Volatiles are evaporated and water added to the residue. This solution is cooled to 0 °C and the pH adjusted to ~3 with conc. HCl. The solution is extracted with Et_2O (3x) to give the crude β -ketonitrile intermediate. The crude β -ketonitrile (1 equiv) is treated with EtOH (0.3 M) and hydrazine hydrate (1.3 equiv) and stirred at 70 °C for 15 h. Volatiles are evaporated and the crude residue is purified by flash column chromatography (1/9 MeOH/ CH_2Cl_2) to give the required pyrazole whose structure

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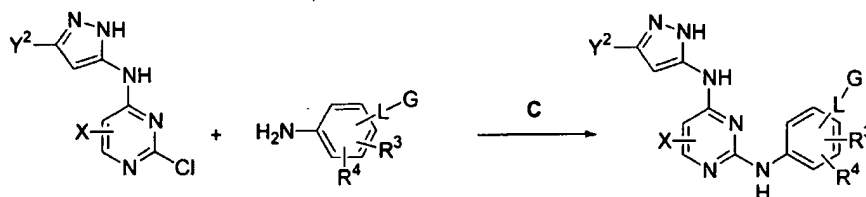
is confirmed by LC/MS and ^1H NMR.

General Method B. Coupling of 5-amino-3-substituted pyrazoles with 5-substituted-2,4-dichloropyrimidines



- 5 A solution of 5-substituted-2,4-dichloropyrimidine (1 equiv), KOAc (1.3 equiv) and 5-amino-3-substituted pyrazole (1.1 equiv) in THF/H₂O (2/1, 0.15 M) is heated at 40 °C for 24 h. The reaction mixture is allowed to cool to rt, dissolved in EtOAc and washed with aqueous NaHCO₃. The combined organic layers are dried (MgSO₄) and concentrated under reduced pressure. The resulting crude solid is purified either by silica gel column chromatography or washing with other solvents to afford the *N*-(3-substituted-1*H*-pyrazol-5-yl)-2-chloro-5-substituted-4-pyrimidinamine intermediate whose structure is confirmed by LC/MS and ^1H NMR.

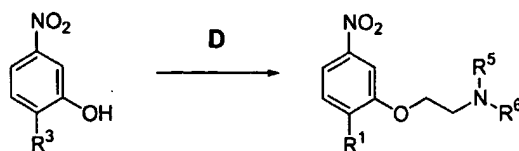
- 15 **General Method C. Coupling of substituted anilines with *N*-(3-substituted-1*H*-pyrazol-5-yl)-2-chloro-5-substituted-4-pyrimidinamines**



- 20 A solution of *N*-(3-substituted-1*H*-pyrazol-5-yl)-2-chloro-5-substituted-4-pyrimidinamine (1 equiv) and a substituted aniline (1 equiv) in an alcohol such as *n*-BuOH (0.08 M) with a catalytic amount of conc. HCl is heated at 100 °C for 24 h. The reaction is cooled to rt then concentrated under reduced pressure. The crude residue is dissolved in CH₂Cl₂ and washed with aqueous NaHCO₃. The combined organic layers are dried (MgSO₄) and concentrated under reduced pressure. Preparative thin-layer silica gel chromatography, silica gel column chromatography, and/or preparative HPLC are used to purify final products. LC/MS and ^1H

NMR spectroscopy are used to confirm the structures of the final 2,4-substituted pyrimidinediamines.

5 **General Method D. Preparation of substituted-nitrophenoxyamines from substituted-nitrophenols**



10 A slurry of 3-nitrophenol (1 equiv) and NaOH pellets (1 equiv) in H₂O (7 M) is stirred for ten min after which time *p*-xylene (1.4 M), K₂CO₃ (1.5 equiv) and aminoethylchloride·HCl (1 equiv) are added and the reaction heated to 100 °C for 4 h. The reaction was cooled to rt then concentrated under reduced pressure. The crude residue is dissolved in *p*-xylene and washed with 1N NaOH (2x) and H₂O (1x). The organic layer is dried (MgSO₄) and concentrated *in vacuo* to furnish the resulting crude material whose structure is confirmed by
15 LC/MS and ¹H NMR.

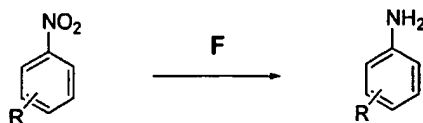
General Method E. Hydrogenation of substituted nitrobenzenes with palladium to substituted anilines



20 A solution of the substituted nitrobenzene (1 equiv) in ethanol (0.2 M) is added via syringe to a flask containing palladium on carbon (10 mol%). The reaction vessel is fitted with a balloon adapter and charged with hydrogen and evacuated three times until the reaction is under a H₂ atmosphere. The reaction is allowed to stir overnight and then purged with Ar and evacuated three times until an Ar atmosphere has been achieved. The reaction solution
25 is filtered through a pad of Celite and washed with copious amounts of ethanol. The filtrate

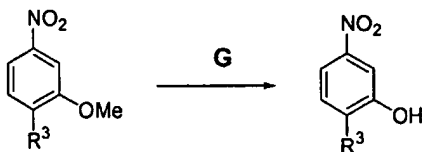
is concentrated in vacuo to afford the desired aniline whose structure is confirmed by LC/MS and ^1H NMR.

General Method F. Hydrogenation of substituted nitrobenzenes with tin chloride to substituted anilines



A solution of intermediate nitro derivative (1 equiv) and SnCl_2 (6 equiv) in ethanol (0.18 M) is heated to reflux over 4h. The reaction mixture is allowed to cool to rt, concentrated and dissolved in EtOAc. Satd NaHCO_3 is then added to precipitate the tin salts. The liquid is decanted and poured into a separatory funnel, diluted with EtOAc and washed with H_2O . The combined organic layers are dried (MgSO_4) and filtered. The filtrate is concentrated in vacuo to afford the intermediate aniline whose structure is confirmed by LC/MS and ^1H NMR.

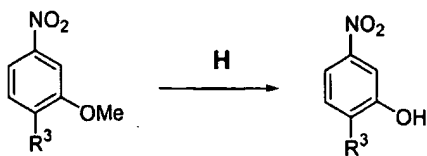
General Method G. Deprotection of substituted nitroanisole with borontribromide



To a solution of 2-substituted-5-nitroanisole (1 equiv) in CH_2Cl_2 (0.12 M) is added borontribromide (1.0 M in CH_2Cl_2 , 1 equiv) at -65°C . The reaction is slowly allowed to reach room temperature and stir for 16 h. The reaction mixture is quenched slowly with H_2O , poured into a separatory funnel and extracted with CH_2Cl_2 . The combined organic layers are washed with satd NaHCO_3 , dried (MgSO_4), filtered and concentrated in vacuo to give crude organic residue. The residue is purified by flash silica column chromatography using 10%EtOAc/90%Hex as eluent to afford the desired phenol whose structure is

confirmed by LC/MS and ^1H NMR.

General Method H. Deprotection of substituted nitroanisole with hydrogen bromide

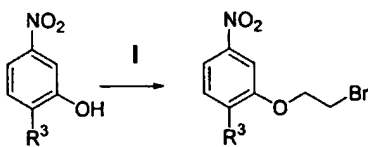


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To a solution of 48% HBr (0.5 M) is added 2-substituted-5-nitroanisole (1 equiv). The solution is heated at reflux for 3 d. The reaction mixture is allowed to cool to rt, diluted with H₂O, and extracted with EtOAc. The organic layer is dried (MgSO₄), filtered and concentrated in vacuo to give crude organic residue. Purification by silica gel column chromatography using 20%EtOAc/80%Hex as eluent affords the desired phenol whose structure is confirmed by LC/MS and ^1H NMR.

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General Method I. Preparation of substituted 2-bromoethoxy-nitrobenzenes



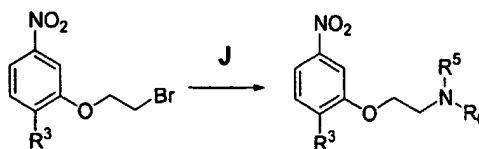
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To a solution of substituted 3-nitrophenol (1 equiv) in acetonitrile (0.72 M) is added 1,2-dibromoethane (1 equiv) and Cs₂CO₃ (3 equiv). The mixture is refluxed overnight. After cooling to rt, the reaction mixture is diluted by EtOAc and washed with 1N NaOH (3x), water (1x) and brine (2x). The organic layer is dried (MgSO₄) and concentrated in vacuo to afford the crude product whose structure is confirmed by ^1H NMR and which is used without further purification.

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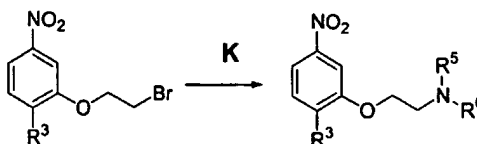
General Method J. Preparation of substituted nitrophenoxyethanamines without sodium iodide

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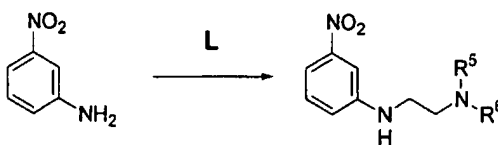
A solution of bromoether intermediate (1 equiv), amine (2 equiv) and K₂CO₃ (8 equiv) in acetone (0.10 M) is heated to 65 °C for 24 h. The reaction mixture is allowed to cool to rt, diluted with EtOAc and washed with H₂O. The organic layer is concentrated in vacuo and the resulting crude solid or oil is purified by silica gel column chromatography to furnish the nitro derivative whose structure is confirmed by LC/MS and ¹H NMR.

General Method K. Preparation of substituted nitrophenoxyethanamines using sodium iodide



A solution of bromoether intermediate (1 equiv), amine (5 equiv), NaI (1 equiv), and Na₂CO₃ (5 equiv) in acetone (0.10 M) is heated to 65 °C for 24 h. The reaction mixture is allowed to cool to rt, evaporated to dryness, diluted with EtOAc, and washed with H₂O. The organic layer is concentrated in vacuo and the resulting crude solid or oil is purified by silica gel column chromatography to furnish the nitro derivative whose structure is confirmed by LC/MS and ¹H NMR.

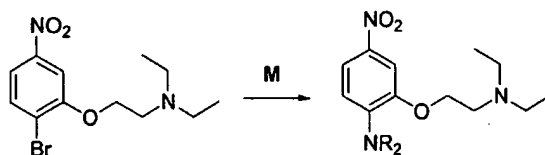
General Method L. Preparation of substituted nitrophenyl-1,2-ethanediamines



To a vigorously stirring mixture of the hydrochloride salt of the chloroamine (1.5 equiv) in Et₂O (1.0 M) is added Et₃N (1 equiv). A white precipitate forms and is filtered off. The

filtrate is concentrated under reduced pressure to obtain an oil. To the resulting free base is added 3-nitroaniline (1 equiv) and xylenes (0.5 M). The reaction mixture is heated to 130 °C for 24 h. After reaction cooling to rt, the mixture is concentrated under reduced pressure. The crude residue is dissolved in 30% EtOAc/Hex and passed through a pad of silica gel to
 5 afford the nitroamine derivative whose structure is confirmed by LC/MS and ¹H NMR.

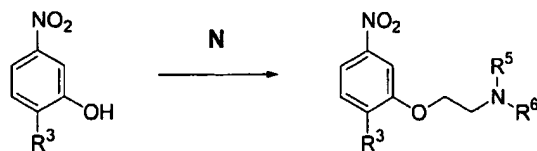
General Method M. Preparatio of amino substituted nitrophenyl-1,2-ethanediamines



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A flask charged with the nitro compound (1 equiv), Pd₂(dba)₃ (0.01 equiv), *rac*-BINAP (0.02 equiv) and Cs₂CO₃ (1.4 equiv) is flushed with Ar before toluene (degassed with Ar, 0.3 M) and the amine (1.2 equiv) are added via syringes to form a red suspension (Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.* **2000**, *65*, 1144). The reaction is heated at 80 °C overnight.
 15 The reaction solution is filtered through a pad of celite and washed with EtOAc. The filtrate is concentrated in vacuo. The residue is purified by flash silica column chromatography (EtOAc/MeOH 9:1) to afford the pure product whose structure is confirmed by LC/MS and ¹H NMR.

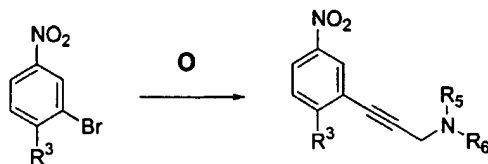
20 **General Method N. Preparation of substituted nitrophenoxyethanamines from substituted nitrophenols.**



25 To a solution of the nitrophenol (1 equiv) and aminoalcohol (1 equiv) in THF (0.20 M) is added PPh₃ (1.5 equiv) and ADDP (1.5 equiv) at ambient temperature. The reaction mixture is allowed to stir overnight under Ar. The mixture is placed in an ice bath and a volume of

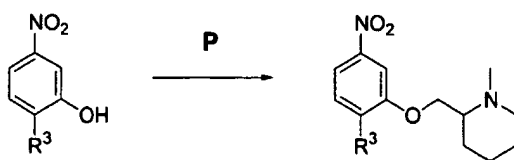
hexanes is added to double the reaction volume. The white precipitate is filtered off and the filtrate is concentrated *in vacuo*. The residue is purified by silica gel column chromatography to furnish the desired nitro derivative whose structure is confirmed by LC/MS and ^1H NMR.

5 **General Method O. Preparation of substituted nitrophenyl-2-propyn-1-amine**



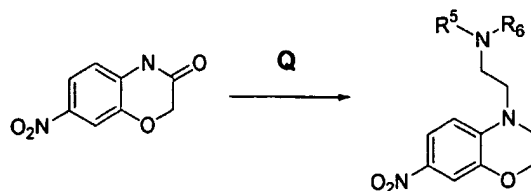
A mixture of aminopropyne (1 equiv), bromonitrobenzene (1.1 equiv), copper(I) iodide (0.25
10 equiv), triphenylphosphine (0.25 equiv), and *trans*-dichlorobis(triphenylphosphine)-palladium(II) (0.25 equiv) in DMF (0.5 M) and Et₃N (0.8 M) is stirred at 80 °C under argon overnight. The mixture is cooled to rt and diluted with EtOAc and water. The layers are separated and the organic phase is washed with brine, dried (MgSO₄), and concentrated in
15 *vacuo*. Purification by column chromatography using 30-70% EtOAc in hexanes as eluent affords the alkyne intermediate whose structure is confirmed by LC/MS and ^1H NMR.

General Method P. Preparation of substituted nitrophenoxymethyl piperidines



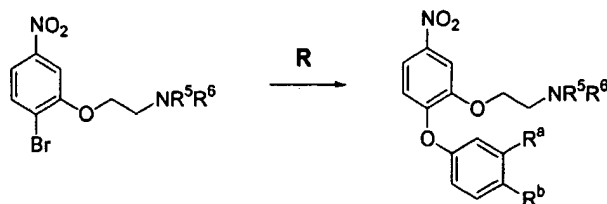
20 A solution of the nitrophenol (1 equiv), 1-methylpiperidine-2-methanol (1.25 equiv) and PPh₃ (1 equiv) is dissolved in THF (0.13 M) and cooled to 0 °C. After 10 min DEAD (1.25 equiv) is added slowly via syringe. The cold bath is removed and the reaction mixture is allowed to stir overnight under Ar at room temperature. The mixture is concentrated and
25 purified by flash silica gel chromatography (5/95 MeOH/CH₂Cl₂) to furnish the intermediate nitro derivative whose structure is confirmed by LC/MS and ^1H NMR.

General Method Q. Preparation of substituted 7-nitro-2,3-dihydro-4H-1,4-benzoxazin-4-yl ethanamines



5 A solution of 7-nitro-2H-1,4-benzoxazin-3(4H)-one (1 equiv) in THF (1.3 M) is cooled to 0 °C and borane-THF complex (1.3 equiv) is added slowly via syringe. The reaction mixture is allowed to warm slowly to rt and then fitted with a reflux condensor and heated to reflux for 2 h. The reaction is cooled, diluted with Et₂O and washed with satd. NaHCO₃. The combined organics are dried (MgSO₄), filtered and concentrated to yield the desired intermediate as a bright orange solid whose structure is confirmed by LC/MS and ¹H NMR. The nitro intermediate (1 equiv) is dissolved in THF (0.1 M), cooled to 0 °C and NaH (2 equiv, 60%wt in mineral oil) is added. The reaction solution is allowed to stir for 5 min and then the substituted aminoethylchloride is added. The cold bath is removed and the reaction is allowed to reach rt. The flask is fitted with a reflux condenser and heated to reflux overnight. The reaction mixture is cooled to rt and quenched with a slow addition of water. The mixture is extracted with EtOAc (3x) and the combined organic layers are dried (MgSO₄), filtered and concentrated. Purification by flash silica chromatography (5/95 MeOH/CH₂Cl₂) furnishes the desired product as a yellow oil whose structure is confirmed by LC/MS and ¹H NMR.

General Method R. Preparation of substituted phenoxy-5-nitrophenoxyethanamines



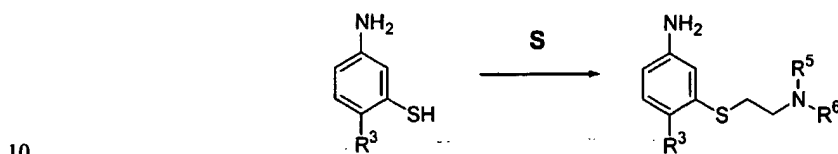
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Nitrophenylbromide (1 equiv), phenol (2 equiv), CsCO₃ (2 equiv), Cu(OTf)₂·PhH (0.03

equiv), 1-naphthoic acid (2 equiv), molecular sieves (5A, 2 equiv), EtOAc (0.05 equiv), and toluene (1.6 M) are combined and heated at 100 °C overnight. The mixture is cooled to ambient temperature before being taken up in CH₂Cl₂. The mixture is washed with 1N NaOH (1x), H₂O (1x), and brine (1x). The organics are dried over Na₂SO₄ and concentrated.

5 Purification by flash silica gel chromatography provides the desired biaryl ether intermediate whose structure is confirmed by LC/MS and ¹H NMR.

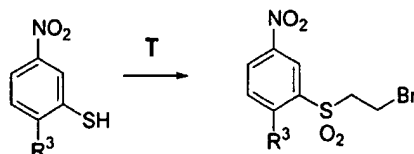
General Method S. Preparation of substituted [[2-(amino)ethyl]sulfanyl]aniline



A slurry of aminothiophenol (1 equiv) and NaOH pellets (1 equiv) in H₂O (7 M) is stirred for ten min, after which time *p*-xylene (1.4 M), K₂CO₃ (1.5 equiv) and aminoethylchloride·HCl (1 equiv) is added and the reaction is heated to 100 °C for 2 h. After cooling to rt, the reaction is concentrated under reduced pressure. The crude residue is dissolved in *p*-xylene and washed with 1N NaOH (2 x) and H₂O (1 x). The organic layer is dried (MgSO₄) and concentrated in vacuo to furnish the resulting crude material whose structure is confirmed by LC/MS and ¹H NMR.

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20 General Method T. Preparation of substituted (2-bromoethyl)sulfonyl-nitrobenzene

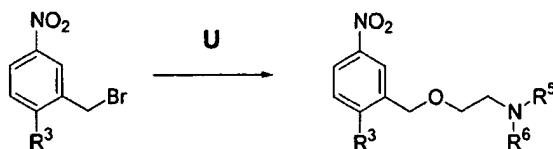


A solution of the nitrothiophenol (1 equiv), 2-bromoethanol (1 equiv) and K₂CO₃ (1.5 equiv) in toluene (0.10 M) is heated to 100 °C for 12 h. The reaction mixture is allowed to cool to rt, diluted with EtOAc and washed with H₂O. The organic layer is dried (MgSO₄) and concentrated in vacuo to furnish the intermediate alcohol product whose structure is

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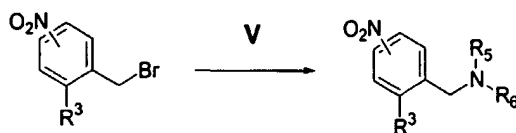
confirmed by LC/MS and ^1H NMR. The crude alcohol (1 equiv) is then dissolved in THF (0.03 M) and treated with CBr_4 (1.25 equiv) and triphenyl phosphine (1.25 equiv). The reaction is left to stir for 1.5 h then another batch of CBr_4 (1.25 equiv) and triphenyl phosphine (1.25 equiv) is added and the mixture is allowed to stir for 1h. The reaction is
5 diluted with H_2O and extracted with EtOAc. The organic layer is dried (MgSO_4), filtered and concentrated in vacuo to give the crude organic residue. Purification by silica gel column chromatography using 20%EtOAc/80%Hex as eluent affords the bromoethyl sulfide intermediate which is confirmed by LC/MS and ^1H NMR. To a rt solution of the sulfide (1 equiv) in acetone (1.1 M) is added OxoneTM (3 equiv). After stirring for 3 days, the reaction
10 is diluted with H_2O and extracted with EtOAc. The organic layer is dried (MgSO_4), filtered and concentrated in vacuo to give the crude bromo phenylsulfone whose structure is confirmed by LC/MS and ^1H NMR. Product is used in subsequent reactions without purification.

15 **General Method U. Preparation of substituted (nitrobenzyl)oxyethanamines**



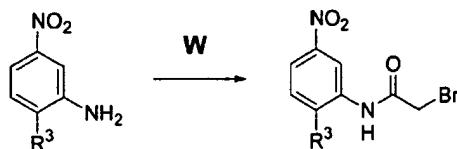
To a solution of the aminoalcohol (1 equiv) in anhydrous DMF (0.2 M) is added NaH (1.5
20 equiv) in one portion, and the reaction mixture is stirred at rt under argon. After 1h, nitrobenzyl bromide (1 equiv) is added and the reaction is stirred for 4h at rt. The reaction is partitioned with 0.2 M HCl and dichloromethane. The organic layer is washed with brine and concentrated under reduced pressure to obtain an oil. The crude residue is purified by MPLC (Biotage) to afford the corresponding intermediate whose structure is confirmed by
25 LC/MS and ^1H NMR.

General Method V. Preparation of substituted nitrophenylmethanamines



A solution of the secondary amine (2 equiv) and nitrobenzyl bromide (1 equiv) in anhydrous THF (0.20 M) is stirred under argon for 15 h. The resultant white precipitate is filtered off
 5 and the filtrate is concentrated *in vacuo*. The reaction is partitioned between water and dichloromethane. The organic layer is washed with brine and concentrated under reduced pressure to obtain an oil. The crude residue is purified by MPLC (Biotage) to afford the corresponding intermediate whose structure is confirmed by LC/MS and ¹H NMR.

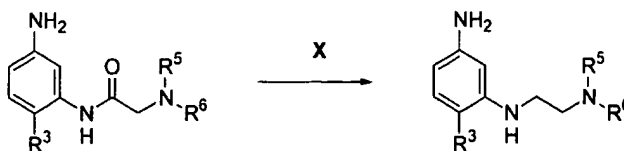
10 **General Method W. Preparation of substituted bromo-N-(nitrophenyl)acetamides**



To a 0 °C suspension of the nitroaniline (1 equiv) and sodium bicarbonate (4 equiv) in
 15 chloroform (1 M) is added bromoacetyl bromide (1.1 equiv) dropwise. The thick suspension is stirred at 0 °C for 30 min. The reaction is then diluted with dichloromethane and water. The layers are separated and the organic phase is washed with brine, dried (MgSO₄), and concentrated *in vacuo* to furnish the intermediate nitro- α -bromoketone derivative whose structure is confirmed by ¹H NMR.

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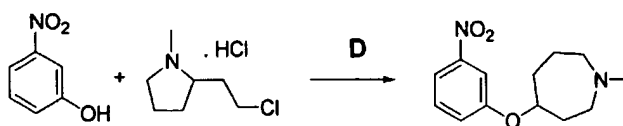
General Method X. Preparation of substituted N¹-[2-(amino)ethyl]-1,3-benzenediamine



A solution of the amide (1 equiv) in THF (0.1 M) is treated with borane dimethylsulfide (5 equiv). The reaction is refluxed under argon overnight at which time it becomes a suspension. The reaction mixture is cooled to rt and quenched with EtOH (15 equiv) and 2 M HCl (6 equiv). The resulting solution is refluxed for 1 h, cooled to rt, and basified with 1 N KOH solution. The product is then extracted with CH₂Cl₂, dried (MgSO₄), and concentrated in vacuo to give crude product. Purification by column chromatography using 2-8% MeOH in CH₂Cl₂ as eluent affords the aniline intermediate whose structure is confirmed by ¹H NMR.

10

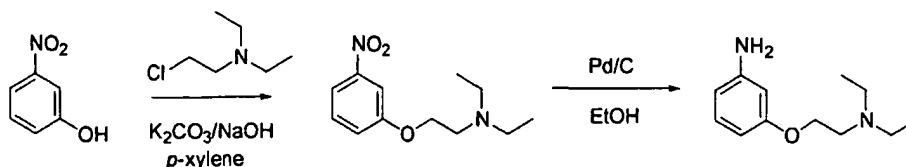
Preparation of 1-methyl-4-(3-nitrophenoxy)azepane

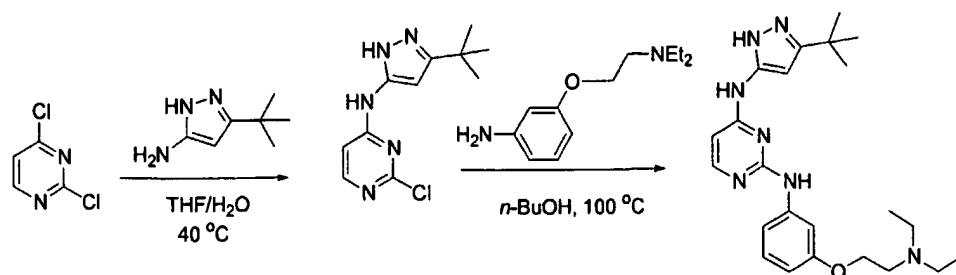


This compound was prepared by the general method described in D using 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride as the starting aminoalkyl halide to give 1-methyl-4-(3-nitrophenoxy)azepane. ¹H NMR (CDCl₃) δ (7.78, d, 1H), (7.68, s, 1H), (7.37, dd, 1H), (7.18, d, 1H), (4.63, m, 1H), (2.72, m, 1H), (2.63, m, 2H), (2.55, m, 1H), (2.33, s, 3H), (2.16, m, 2H), (1.96, m, 1H), (1.87, m, 2H), (1.36, m, 1H); MS (ESI-MS) 251 (M+H)⁺.

20

Example 1: Preparation of N⁴-(3-tert-butyl-1H-pyrazol-5-yl)-N²-{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidinediamine





A slurry of 3-nitrophenol (1.0 g, 7.19 mmol) and NaOH pellets (288 mg, 7.19 mmol) in H₂O (1 mL) was stirred for 10 min after which time *p*-xylene (5 mL), K₂CO₃ (1.5 g, 10.78 mmol) and 2-diethylaminoethylchloride:HCl (1.24 g, 7.19 mmol) were added and the mixture was heated to 100 °C for 4 h. The reaction was cooled to rt then concentrated under reduced pressure. The crude residue was dissolved in *p*-xylene (20 mL) and washed with 1N NaOH (2 x 20 mL) and H₂O (1 x 20 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure to yield 1.51 g (88%) of *N,N*-diethyl-*N*-[2-(3-nitrophenoxy)ethyl]amine as a solid. ¹H NMR (300 MHz, CDCl₃) δ 7.81-7.76 (m, 1H), 7.73-7.72 (m, 1H), 7.40 (t, *J* = 8.1 Hz, 1H), 7.23-7.19 (m, 1H), 4.09 (t, *J* = 6.2 Hz, 2H), 2.88 (t, *J* = 5.9 Hz, 2H), 2.63 (q, *J* = 6.92 Hz, 4H), 1.60 (t, *J* = 6.8 Hz, 6H); MS (ESI-MS) 239 (M+H)⁺.

A solution of *N,N*-diethyl-*N*-[2-(3-nitrophenoxy)ethyl]amine (1.5 g, 6.30 mmol) in ethanol (35 mL) was added via syringe to a flask containing palladium on carbon (150 mg). The reaction vessel was fitted with a balloon adapter and charged with hydrogen and evacuated three times until the reaction was under a H₂ atmosphere. The reaction was allowed to stir overnight and then purged with Ar and evacuated three times until an Ar atmosphere had been achieved. The reaction solution was filtered through a pad of Celite and washed with copious amounts of ethanol. The filtrate was concentrated in vacuo to afford 1.27 g (97%) of 3-[2-(diethylamino)ethoxy]aniline as an oil. ¹H NMR (300 MHz, CDCl₃) δ 7.02 (t, *J* = 8.2 Hz, 1H), 6.32-6.22 (m, 3H), 3.98 (t, *J* = 6.4 Hz, 2H), 2.83 (t, *J* = 6.4 Hz, 2H), 2.60 (q, *J* = 6.81 Hz, 4H), 1.04 (t, *J* = 6.9 Hz, 6H); MS (ESI-MS) 209 (M+H)⁺.

A solution of 2,4-dichloropyrimidine (11.92 g, 80.0 mmol), KOAc (9.42 g, 96.0 mmol, 1.2 equiv) and 5-amino-3-*tert*-butylpyrazole (11.14 g, 80.0 mmol) in THF/H₂O (225 mL, 2/1) was heated at 45 °C for 24 h. The reaction mixture was allowed to cool to rt, dissolved in EtOAc (200 mL) and washed with aqueous NaHCO₃ (2 x 200 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The

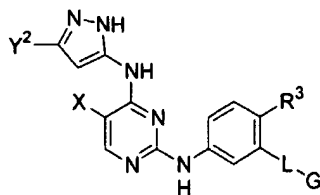
resulting crude solid was purified by silica gel column chromatography (MeOH/CH₂Cl₂, 1/19) to give 8.62 (43%) of *N*-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-2-chloro-4-pyrimidinamine. ¹H NMR (300 MHz, DMSO) δ 12.2 (s, 1H), 10.3 (s, 1H), 8.16 (s, 1 H), 1.26 (s, 9H); Mp>250 °C; MS (ESI-MS) 252 (M+H)⁺. *t*_R 2.20 min. (10-90% CH₃CN/H₂O).

5 A solution of *N*-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-2-chloro-4-pyrimidinamine (6.0 g, 23.84 mmol) and *N*-[2-(3-aminophenoxy)ethyl]-*N,N*-diethylamine (5.0 g, 23.84 mmol) in *n*-BuOH (160 mL) with conc. HCl (2 mL) was heated at 100 °C for 48 h. The reaction was cooled to rt and a precipitate formed. The reaction mixture was filtered and the filtercake washed with *n*-BuOH (100 mL). The resulting white solid was dissolved in CH₂Cl₂ (150
10 mL) and washed with aqueous NaHCO₃ (2 x 150 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure and dried in a vacuum oven overnight to afford 7.2 (70%) of *N*⁴-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-*N*²-{3-[2-(diethylamino)-ethoxy]phenyl}-2,4-pyrimidine-diamine as a solid. ¹H NMR (300 MHz, CD₃OD) δ 7.94 (br s, 1H), 7.26 (br s, 1H), 7.18 (br s, 1 H), 6.59-6.56 (m, 1H), 6.35-6.28 (m, 2H), 4.08 (t, *J* = 5.9
15 Hz, 2H), 2.90 (t, *J* = 5.8 Hz, 2H), 2.67 (q, *J* = 7.1 Hz, 4H), 1.30 (t, *J* = 7.4 Hz, 9H), 1.08 (t, 6H); Mp=160 °C MS (ESI-MS) 424 (M+H)⁺; *t*_R 1.74 min (10-90% CH₃CN/H₂O).

The compounds of examples 2-220 were prepared by general method C where a heterocyclic substituted pyrimidine (prepared by general methods A and B) is reacted with an aniline sidechain (prepared by general methods D-X):

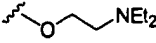
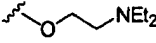

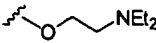

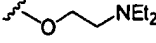

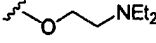

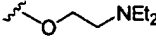

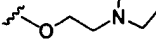

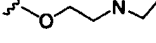

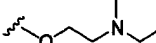

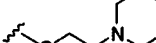

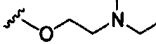

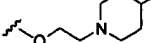
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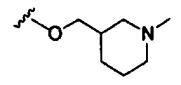

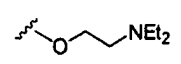

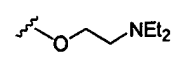

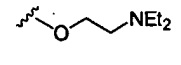

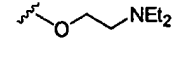

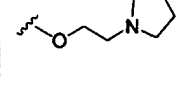

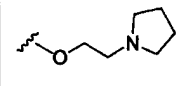

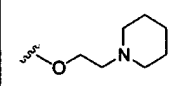

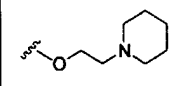

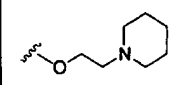
Table 1. Compounds Prepared by general method C.


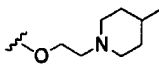

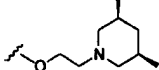

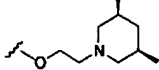

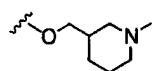

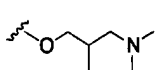

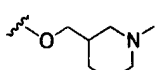
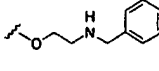
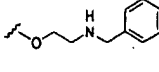
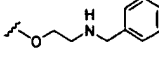


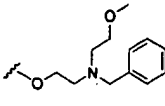
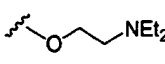
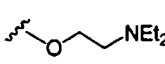
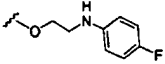
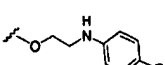
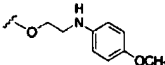
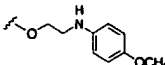
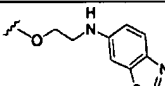
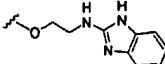
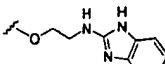
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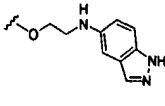
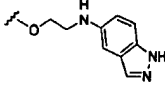
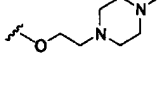
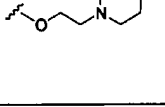
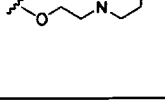
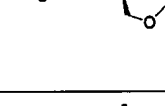
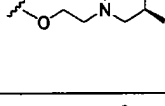
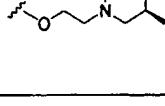
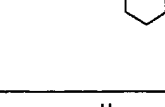

Example	X	Y ²	R ³	L-G	Preparation of Aniline Sidechain	Characterization ^a
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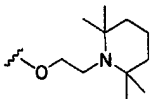
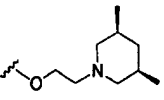
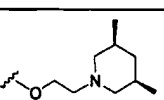
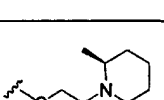
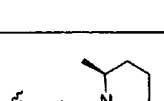
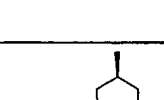
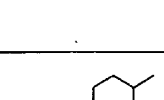
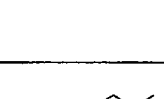
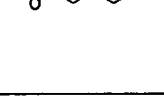
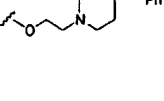
2	H	<i>t</i> -butyl	CN		D, E	(M+H) ⁺ 449 <i>t</i> _R 1.88 min. ^b
3	F	<i>t</i> -butyl	CN		D, E	(M+H) ⁺ 467 <i>t</i> _R 2.09 min. ^b
4	H		H		D, E	(M+H) ⁺ 438 <i>t</i> _R 1.87 min. ^b
5	H		OMe		D, E	(M+H) ⁺ 468 <i>t</i> _R 1.80 min. ^b
6	F		OMe		D, E	(M+H) ⁺ 486 <i>t</i> _R 1.91 min. ^b
7	H		CN		D, E	(M+H) ⁺ 463 <i>t</i> _R 1.95 min. ^b
8	H		OMe		I, K, E	(M+H) ⁺ 466 <i>t</i> _R 1.94 min. ^b
9	F		OMe		I, K, E	(M+H) ⁺ 484 <i>t</i> _R 1.93 min. ^b
10	H		H		I, K, E	(M+H) ⁺ 450 <i>t</i> _R 1.84 min. ^b
11	H		OMe		I, K, E	(M+H) ⁺ 480 <i>t</i> _R 1.92 min. ^b
12	F		OMe		I, K, E	(M+H) ⁺ 498 <i>t</i> _R 1.94 min. ^b
13	H		H		I, K, E	(M+H) ⁺ 464 <i>t</i> _R 2.11 min. ^b

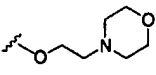
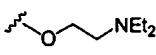
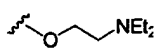
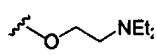
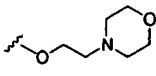
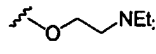
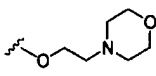
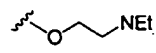
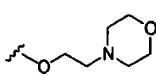
14	H		H		P, E	(M+H) ⁺ 450 <i>t</i> _R 2.05 min. ^b
15	H		H		D, E	(M+H) ⁺ 452 <i>t</i> _R 1.91 min. ^b
16	H		OMe		D, E	(M+H) ⁺ 482 <i>t</i> _R 1.90 min. ^b
17	F		OMe		D, E	(M+H) ⁺ 500 <i>t</i> _R 1.97 min. ^b
18	H		CN		D, E	(M+H) ⁺ 477 <i>t</i> _R 2.03 min. ^b
19	H		OMe		I, K, E	(M+H) ⁺ 480 <i>t</i> _R 2.02 min. ^b
20	F		OMe		I, K, E	(M+H) ⁺ 498 <i>t</i> _R 2.03 min. ^b
21	H		H		I, K, E	(M+H) ⁺ 464 <i>t</i> _R 1.96 min. ^b
22	H		OMe		I, K, E	(M+H) ⁺ 494 <i>t</i> _R 1.98 min. ^b
23	F		OMe		I, K, E	(M+H) ⁺ 512 <i>t</i> _R 2.03 min. ^b

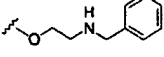
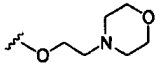
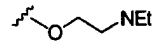
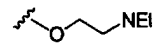
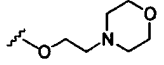
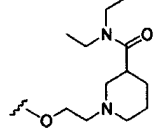
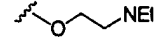
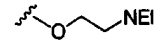
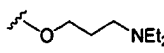
24	H		H		I, K, E	(M+H) ⁺ 478 <i>t</i> _R 2.19 min. ^b
25	H		H		I, K, E	(M+H) ⁺ 492 <i>t</i> _R 2.17 min. ^b
26	H		CH ₃		I, K, E	(M+H) ⁺ 506 <i>t</i> _R 2.25 min. ^b
27	H		H		P, E	(M+H) ⁺ 464 <i>t</i> _R 2.12 min. ^b
28	H		H		P, E	(M+H) ⁺ 420 <i>t</i> _R 1.71 min. ^b
29	F		H		P, E	(M+H) ⁺ 438 <i>t</i> _R 1.75 min. ^b
30	CH ₃	<i>t</i> -butyl	H		D, F	(M+H) ⁺ 472 <i>R</i> _f = 0.23 (85/15 CH ₂ Cl ₂ /MeOH)
31	H	<i>t</i> -butyl	H		D, F	(M+H) ⁺ 458 <i>R</i> _f = 0.21 (85/15 CH ₂ Cl ₂ /MeOH)
32	Br	<i>t</i> -butyl	H		D, F	(M+H) ⁺ 536 <i>R</i> _f = 0.29 (9/1 CH ₂ Cl ₂ /MeOH)

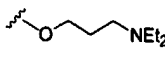
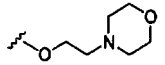
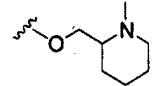
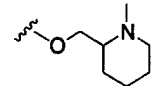

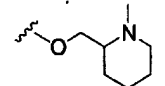

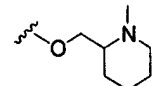

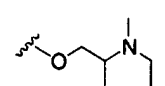

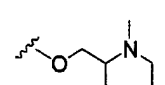
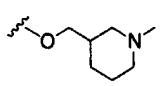
33	H	<i>t</i> -butyl	H		D, F	(M+H) ⁺ 516 $R_f = 0.36$ (9/1 CH ₂ Cl ₂ /MeOH)
34	H	<i>t</i> -butyl	Br		D, H, F	(M+H) ⁺ 502 $R_f = 0.26$ (85/15 CH ₂ Cl ₂ /MeOH)
35	F	<i>t</i> -butyl	Br		D, H, F	(M+H) ⁺ 520 $R_f = 0.35$ (85/15 CH ₂ Cl ₂ /MeOH)
36	H	<i>t</i> -butyl	H		I, J, E	(M+H) ⁺ 462 $R_f = 0.20$ (95/5 CH ₂ Cl ₂ /MeOH)
37	F	<i>t</i> -butyl	H		I, J, E	(M+H) ⁺ 480 $R_f = 0.40$ (9/1 CH ₂ Cl ₂ /MeOH)
38	H	<i>t</i> -butyl	H		I, J, E	(M+H) ⁺ 474 $R_f = 0.37$ (9/1 CH ₂ Cl ₂ /MeOH)
39	F	<i>t</i> -butyl	H		I, J, E	(M+H) ⁺ 492 $R_f = 0.44$ (9/1 CH ₂ Cl ₂ /MeOH)
40	H	<i>t</i> -butyl	H		I, J, F	(M+H) ⁺ 501 $R_f = 0.49$ (85/15 CH ₂ Cl ₂ /MeOH)
41	H	<i>t</i> -butyl	H		I, J, F	(M+H) ⁺ 484 $R_f = 0.17$ (85/15 CH ₂ Cl ₂ /MeOH)
42	F	<i>t</i> -butyl	H		I, J, F	(M+H) ⁺ 502 $R_f = 0.32$ (85/15 CH ₂ Cl ₂ /MeOH)

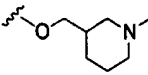
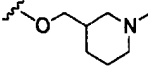

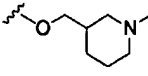

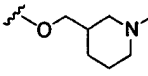

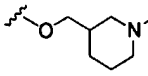

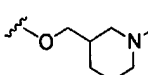

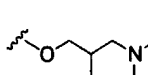

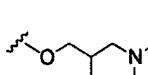
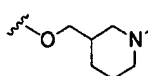
43	H	<i>t</i> -butyl	H		I, J, F	(M+H) ⁺ 484 <i>R_f</i> = 0.26 (9/1 CH ₂ Cl ₂ /MeOH)
44	F	<i>t</i> -butyl	H		I, J, F	(M+H) ⁺ 502 <i>R_f</i> = 0.36 (9/1 CH ₂ Cl ₂ /MeOH)
45	H	<i>t</i> -butyl	H		I, J, E	(M+H) ⁺ 451 <i>t_R</i> 1.63 min. ^b
46	CH ₃	<i>t</i> -butyl	H		I, J, E	(M+H) ⁺ 465 <i>R_f</i> = 0.14 (85/15 CH ₂ Cl ₂ /MeOH)
47	Br	<i>t</i> -butyl	H		I, J, E	(M+H) ⁺ 529 <i>R_f</i> = 0.20 (85/15 CH ₂ Cl ₂ /MeOH)
48	H	<i>t</i> -butyl	H		I, J, E	(M+H) ⁺ 466 <i>R_f</i> = 0.30 (85/15 CH ₂ Cl ₂ /MeOH)
49	H	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 464 <i>R_f</i> = 0.21 (9/1 CH ₂ Cl ₂ /MeOH)
50	F	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 482 <i>R_f</i> = 0.27 (9/1 CH ₂ Cl ₂ /MeOH)
51	H	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 450 <i>R_f</i> = 0.25 (85/15 CH ₂ Cl ₂ /MeOH)
52	F	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 468 <i>R_f</i> = 0.36 (85/15 CH ₂ Cl ₂ /MeOH)

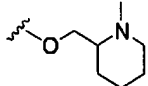
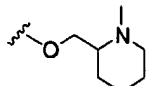
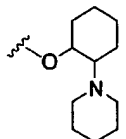
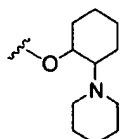
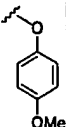
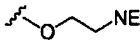
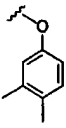
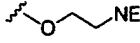
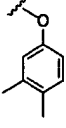
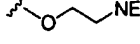
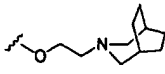
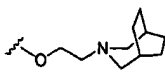
53	H	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 492 <i>R_f</i> = 0.17 (9/1 CH ₂ Cl ₂ /MeOH)
54	H	<i>t</i> -butyl	CH ₃		I, K, E	(M+H) ⁺ 478 <i>R_f</i> = 0.17 (9/1 CH ₂ Cl ₂ /MeOH)
55	F	<i>t</i> -butyl	CH ₃		I, K, E	(M+H) ⁺ 496 <i>R_f</i> = 0.32 (9/1 CH ₂ Cl ₂ /MeOH)
56	H	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 464 <i>R_f</i> = 0.14 (9/1 CH ₂ Cl ₂ /MeOH)
57	F	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 482 <i>R_f</i> = 0.22 (9/1 CH ₂ Cl ₂ /MeOH)
58	H	<i>t</i> -butyl	CH ₃		I, K, E	(M+H) ⁺ 478 <i>R_f</i> = 0.20 (9/1 CH ₂ Cl ₂ /MeOH)
59	H	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 450 <i>R_f</i> = 0.23 (9/1 CH ₂ Cl ₂ /MeOH)
60	F	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 468 <i>R_f</i> = 0.18 (9/1 CH ₂ Cl ₂ /MeOH)
61	H	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 526 <i>R_f</i> = 0.25 (9/1 CH ₂ Cl ₂ /MeOH)
62	F	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 545 <i>R_f</i> = 0.39 (9/1 CH ₂ Cl ₂ /MeOH)

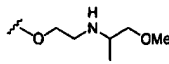
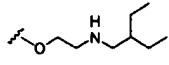
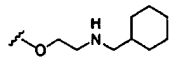
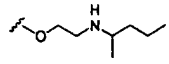
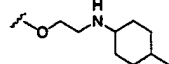
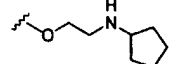
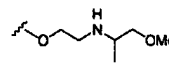
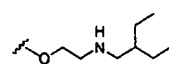
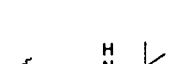
63	F	<i>t</i> -butyl	OMe		D, E	(M+H) ⁺ 486 <i>t</i> _R 1.69 min. ^b
64	Br	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 502 <i>t</i> _R 1.91 min. ^b
65	CH ₃	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 438 <i>t</i> _R 1.79 min. ^b
66	F	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 442 <i>t</i> _R 1.74 min. ^b
67	F	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 456 <i>t</i> _R 1.69 min. ^b
68	Cl	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 458 <i>t</i> _R 1.87 min. ^b
69	Cl	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 472 <i>t</i> _R 1.81 min. ^b
70	H	<i>t</i> -butyl	Cl		D, E	(M+H) ⁺ 458 <i>t</i> _R 1.91 min. ^b
71	Br	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 518 <i>R</i> _f = 0.5 (9/1 CH ₂ Cl ₂ /MeOH)

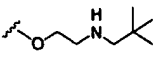
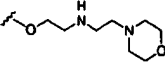
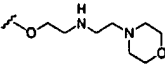
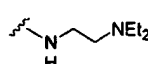
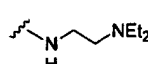
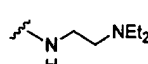
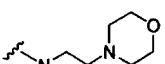
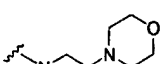

72	F	<i>t</i> -butyl	H		D, F	(M+H) ⁺ 476 <i>t</i> _R 1.83 min. ^b
73	CH ₃	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 452 <i>R</i> _f = 0.41 (9/1 CH ₂ Cl ₂ /MeOH)
74	H	<i>t</i> -butyl	OMe		D, E	(M+H) ⁺ 454 <i>t</i> _R 1.75 min. ^b
75	F	<i>t</i> -butyl	OMe		D, E	(M+H) ⁺ 472 <i>t</i> _R 1.69 min. ^b
76	H	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 438 <i>R</i> _f = 0.4 (9/1 CH ₂ Cl ₂ /MeOH)
77	H	<i>t</i> -butyl	H		I, J, E	(M+H) ⁺ 535 <i>t</i> _R 2.01 min. ^b
78	H	<i>t</i> -butyl	CH ₃		D, E	(M+H) ⁺ 438 <i>t</i> _R 1.70 min. ^b
79	F	<i>t</i> -butyl	CH ₃		D, E	(M+H) ⁺ 456 <i>t</i> _R 1.69 min. ^b
80	H	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 438 <i>t</i> _R 1.65 min. ^b

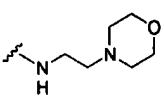
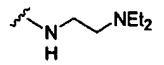
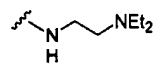
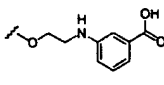
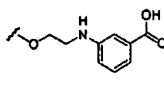
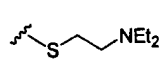
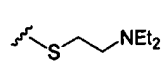
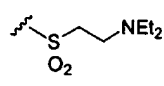
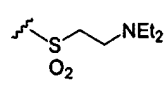
81	F	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 456 <i>t</i> _R 1.67 min. ^b
82	F	<i>t</i> -butyl	CH ₃		D, E	(M+H) ⁺ 470 <i>t</i> _R 1.85 min. ^b
83	H	<i>t</i> -butyl	CH ₃		P, E	(M+H) ⁺ 450 <i>t</i> _R 2.17 min. ^b
84	F	<i>t</i> -butyl	CH ₃		P, E	(M+H) ⁺ 468 <i>t</i> _R 2.02 min. ^b
85	H		CH ₃		P, E	(M+H) ⁺ 464 <i>t</i> _R 2.14 min. ^b
86	F		CH ₃		P, E	(M+H) ⁺ 482 <i>t</i> _R 2.12 min. ^b
87	H		CH ₃		P, E	(M+H) ⁺ 478 <i>t</i> _R 2.23 min. ^b
88	F		CH ₃		P, E	(M+H) ⁺ 496 <i>t</i> _R 2.21 min. ^b
89	F	<i>t</i> -butyl	H		P, E	(M+H) ⁺ 454 <i>t</i> _R 2.00 min. ^b

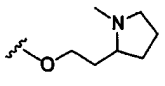
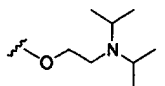
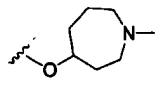
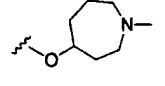
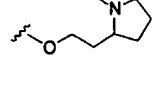
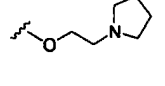
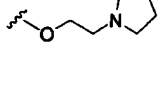
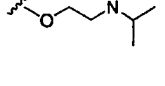
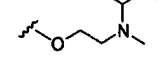
90	H	<i>t</i> -butyl	OMe		P, E	(M+H) ⁺ 466 <i>t</i> _R 1.80 min. ^b
91	F	<i>t</i> -butyl	OMe		P, E	(M+H) ⁺ 484 <i>t</i> _R 1.81 min. ^b
92	H		OMe		P, E	(M+H) ⁺ 480 <i>t</i> _R 2.01 min. ^b
93	F		OMe		P, E	(M+H) ⁺ 498 <i>t</i> _R 2.03 min. ^b
94	F		H		P, E	(M+H) ⁺ 468 <i>t</i> _R 2.00 min. ^b
95	F		OMe		P, E	(M+H) ⁺ 512 <i>t</i> _R 2.02 min. ^b
96	F		H		P, E	(M+H) ⁺ 482 <i>t</i> _R 2.09 min. ^b
97	H		OMe		P, E	(M+H) ⁺ 494 <i>t</i> _R 2.01 min. ^b
98	H	<i>t</i> -butyl	H		P, E	(M+H) ⁺ 436 <i>t</i> _R 1.97 min. ^b

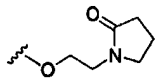
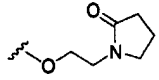
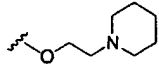
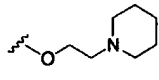
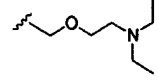
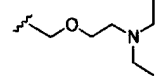
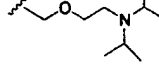
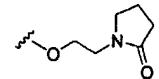
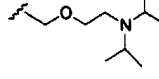
99	H	<i>t</i> -butyl	H		P, E	(M+H) ⁺ 436 <i>t</i> _R = 1.81 min. ^b
100	F	<i>t</i> -butyl	H		P, E	(M+H) ⁺ 454 <i>t</i> _R 1.97 min. ^b
101	H	<i>t</i> -butyl	OMe		N, E	(M+H) ⁺ 520 <i>R</i> _f = 0.04 (9/1 CH ₂ Cl ₂ /MeOH)
102	F	<i>t</i> -butyl	OMe		N, E	(M+H) ⁺ 538 <i>R</i> _f = 0.09 (9/1 CH ₂ Cl ₂ /MeOH)
103	F	<i>t</i> -butyl			I, R, E	(M+H) ⁺ 564 <i>R</i> _f = 0.07 (8/2 CH ₂ Cl ₂ /MeOH)
104	H	<i>t</i> -butyl			I, R, E	(M+H) ⁺ 544 <i>R</i> _f = 0.08 (8/2 CH ₂ Cl ₂ /MeOH)
105	F	<i>t</i> -butyl			I, R, E	(M+H) ⁺ 562 <i>R</i> _f = 0.08 (8/2 CH ₂ Cl ₂ /MeOH)
106	F	<i>t</i> -butyl	Me		I, K, E	(M+H) ⁺ 508 <i>R</i> _f = 0.55 (50/49/1 MeOH/CH ₃ CN/H ₂ O)
107	H	<i>t</i> -butyl	Me		I, K, E	(M+H) ⁺ 490 <i>R</i> _f = 0.40 (50/49/1 MeOH/CH ₃ CN/H ₂ O)

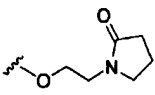
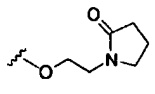
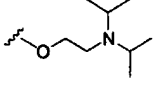
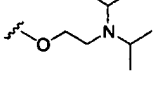
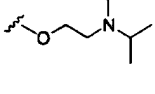
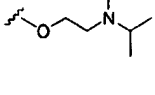
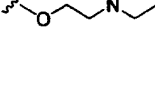
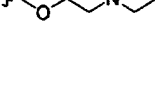
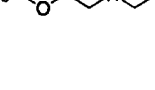
108	H	<i>t</i> -butyl	OMe		I, K, E	(M+H) ⁺ 470 <i>R_f</i> = 0.27 (3/2 EtOAc/MeOH)
109	F	<i>t</i> -butyl	OMe		I, K, E	(M+H) ⁺ 500 <i>R_f</i> = 0.44 (3/2 EtOAc/MeOH)
110	H	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 464 <i>R_f</i> = 0.33 (3/2 EtOAc/MeOH)
111	H	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 438 <i>R_f</i> = 0.33 (3/2 EtOAc/MeOH)
112	H	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 464 <i>R_f</i> = 0.28 (3/2 EtOAc/MeOH)
113	H	<i>t</i> -butyl	H		I, K, E	(M+H) ⁺ 436 <i>R_f</i> = 0.33 (3/2 EtOAc/MeOH)
114	F	<i>t</i> -butyl	OMe		I, K, E	(M+H) ⁺ 488 <i>R_f</i> = 0.38 (3/2 EtOAc/MeOH)
115	H	<i>t</i> -butyl	OMe		I, K, E	(M+H) ⁺ 482 <i>R_f</i> = 0.24 (3/2 EtOAc/MeOH)
116	F	<i>t</i> -butyl	OMe		I, K, E	(M+H) ⁺ 468 <i>R_f</i> = 0.47 (3/2 EtOAc/MeOH)

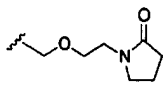
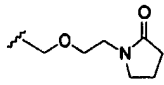
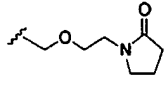
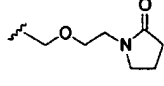
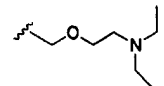
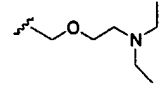
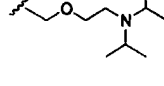
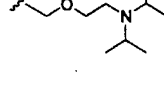
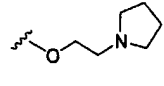
117	H	<i>t</i> -butyl	OMe		I, K, E	(M+H) ⁺ 486 <i>R_f</i> = 0.35 (3/2 EtOAc/MeOH)
118	H	<i>t</i> -butyl	OMe		I, K, E	(M+H) ⁺ 511 <i>R_f</i> = 0.18 (3/2 EtOAc/MeOH)
119	F	<i>t</i> -butyl	OMe		I, K, E	(M+H) ⁺ 529 <i>R_f</i> = 0.29 (3/2 EtOAc/MeOH)
120	H	<i>t</i> -butyl	H		L, E	(M+H) ⁺ 423 <i>R_f</i> = 0.06 (4/1 CH ₂ Cl ₂ /MeOH)
121	CH ₃	<i>t</i> -butyl	H		L, E	(M+H) ⁺ 437 <i>R_f</i> = 0.07 (4/1 CH ₂ Cl ₂ /MeOH)
122	Br	<i>t</i> -butyl	H		L, E	(M+H) ⁺ 501 <i>R_f</i> = 0.14 (4/1 CH ₂ Cl ₂ /MeOH)
123	Br	<i>t</i> -butyl	H		L, E	(M+H) ⁺ 515 <i>R_f</i> = 0.33 (9/1 CH ₂ Cl ₂ /MeOH)
124	H	<i>t</i> -butyl	H		L, E	(M+H) ⁺ 437 <i>R_f</i> = 0.11 (9/1 CH ₂ Cl ₂ /MeOH)
125	H	Ph	H		D, E	(M+H) ⁺ 444 <i>R_f</i> = 0.09 (4/1 CH ₂ Cl ₂ /MeOH)

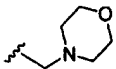
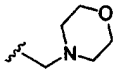
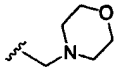
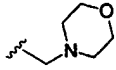
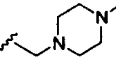
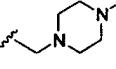
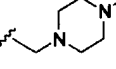
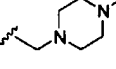
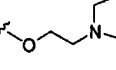
126	CH ₃	<i>t</i> -butyl	H		L, E	(M+H) ⁺ 451 <i>R_f</i> = 0.25 (4/1 CH ₂ Cl ₂ /MeOH)
127	F	<i>t</i> -butyl	H		L, E	(M+H) ⁺ 441 <i>R_f</i> = 0.25 (4/1 CH ₂ Cl ₂ /MeOH)
128	Cl	<i>t</i> -butyl	H		L, E	(M+H) ⁺ 457 <i>R_f</i> = 0.33 (4/1 CH ₂ Cl ₂ /MeOH)
129	H	<i>t</i> -butyl	H		I, J, E	(M+H) ⁺ 488 <i>R_f</i> = 0.33 (9/1 CH ₂ Cl ₂ /MeOH)
130	F	<i>t</i> -butyl	H		I, J, E	(M+H) ⁺ 506 <i>R_f</i> = 0.31 (9/1 CH ₂ Cl ₂ /MeOH)
131	H	<i>t</i> -butyl	H		S	(M+H) ⁺ 440 <i>R_f</i> = 0.25 (4/1 CH ₂ Cl ₂ /MeOH)
132	F	<i>t</i> -butyl	H		S	(M+H) ⁺ 458 <i>R_f</i> = 0.32 (4/1 CH ₂ Cl ₂ /MeOH)
133	H	<i>t</i> -butyl	H		T, J, E	(M+H) ⁺ 472 <i>R_f</i> = 0.33 (9/1 CH ₂ Cl ₂ /MeOH)
134	F	<i>t</i> -butyl	H		T, J, E	(M+H) ⁺ 490 <i>R_f</i> = 0.36 (9/1 CH ₂ Cl ₂ /MeOH)

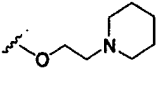
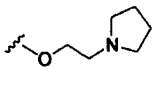
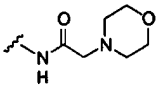
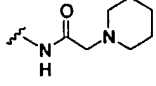
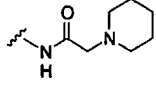
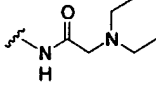
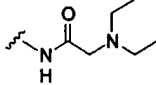
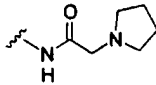
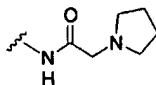
135	F	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 454 <i>t</i> _R 1.83 min. ^c
136	H	<i>t</i> -butyl	H		N, E	(M+H) ⁺ 452 <i>t</i> _R 1.87 min. ^c
137	H	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 436 <i>t</i> _R 1.77 min. ^c
138	F	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 454 <i>t</i> _R 1.83 min. ^c
139	H	<i>t</i> -butyl	H		D, E	(M+H) ⁺ 436 <i>t</i> _R 1.90 min. ^c
140	H	<i>t</i> -butyl	H		N, E	(M+H) ⁺ 422 <i>t</i> _R 1.57 min. ^c
141	F	<i>t</i> -butyl	H		N, E	(M+H) ⁺ 440 <i>t</i> _R 1.83 min. ^c
142	F	<i>t</i> -butyl	H		N, E	(M+H) ⁺ 470 <i>t</i> _R 1.97 min. ^c
143	H	<i>t</i> -butyl	H		N, E	(M+H) ⁺ 458 <i>t</i> _R 2.34 min. ^c

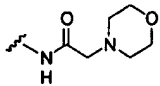
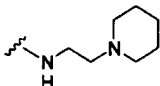
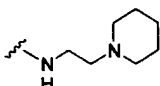
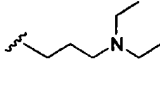
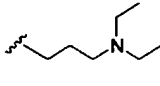
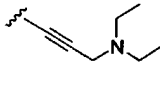
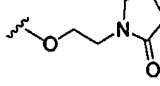
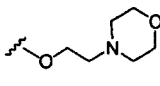

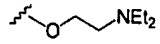
144	H	<i>t</i> -butyl	H		N, E	(M+H) ⁺ 436 <i>t</i> _R 2.12 min. ^c
145	F	<i>t</i> -butyl	H		N, E	(M+H) ⁺ 454 <i>t</i> _R 2.21 min. ^c
146	H	<i>t</i> -butyl	H		N, E	(M+H) ⁺ 436 <i>t</i> _R 1.76 min. ^c
147	F	<i>t</i> -butyl	H		N, E	(M+H) ⁺ 454 <i>t</i> _R 1.83 min. ^c
148	H	<i>t</i> -butyl	H		U, E	(M+H) ⁺ 438 <i>t</i> _R 1.78 min. ^c
149	F	<i>t</i> -butyl	H		U, E	(M+H) ⁺ 456 <i>t</i> _R 1.76 min. ^c
150	H	<i>t</i> -butyl	H		U, E	(M+H) ⁺ 484 <i>t</i> _R 1.85 min. ^c
151	F	<i>t</i> -butyl	OMe		N, E	(M+H) ⁺ 466 <i>t</i> _R 1.95 min. ^c
152	F	<i>t</i> -butyl	H		U, E	(M+H) ⁺ 484 <i>t</i> _R 1.99 min. ^c


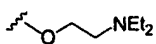
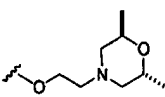
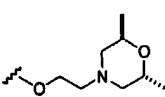
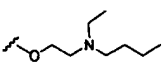
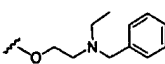
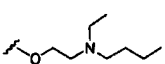
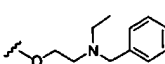
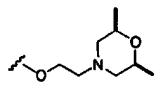
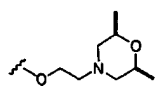
153	H	<i>t</i> -butyl	Me		N, E	(M+H) ⁺ 450 <i>t</i> _R 2.86 min. ^c
154	F	<i>t</i> -butyl	Me		N, E	(M+H) ⁺ 468 <i>t</i> _R 2.90 min. ^c
155	H	<i>t</i> -butyl	OMe		N, E	(M+H) ⁺ 482 <i>t</i> _R 1.73 min. ^c
156	F	<i>t</i> -butyl	OMe		N, E	(M+H) ⁺ 500 <i>t</i> _R 1.83 min. ^c
157	H	<i>t</i> -butyl	Me		N, E	(M+H) ⁺ 466 <i>t</i> _R 1.93 min. ^c
158	F	<i>t</i> -butyl	Me		N, E	(M+H) ⁺ 484 <i>t</i> _R 1.99 min. ^c
159	H	<i>t</i> -butyl	Me		N, E	(M+H) ⁺ 450 <i>t</i> _R 1.91 min. ^c
160	F	<i>t</i> -butyl	Me		N, E	(M+H) ⁺ 468 <i>t</i> _R 1.93 min. ^c
161	H	<i>t</i> -butyl	OMe		N, E	(M+H) ⁺ 466 <i>t</i> _R 1.70 min. ^c


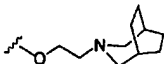

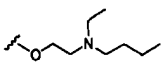

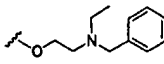

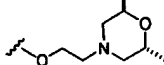

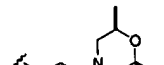
162	H	<i>t</i> -butyl	H		U, E	(M+H) ⁺ 450 <i>t</i> _R 2.00 min. ^c
163	F	<i>t</i> -butyl	H		U, E	(M+H) ⁺ 468 <i>t</i> _R 2.75 min. ^c
164	H	<i>t</i> -butyl	OMe		U, E	(M+H) ⁺ 480 <i>t</i> _R 2.13 min. ^c
165	F	<i>t</i> -butyl	OMe		U, E	(M+H) ⁺ 498 <i>t</i> _R 2.13 min. ^c
166	H	<i>t</i> -butyl	OMe		U, E	(M+H) ⁺ 468 <i>t</i> _R 1.83 min. ^c
167	F	<i>t</i> -butyl	OMe		U, E	(M+H) ⁺ 486 <i>t</i> _R 1.84 min. ^c
168	H	<i>t</i> -butyl	OMe		U, E	(M+H) ⁺ 496 <i>t</i> _R 1.92 min. ^c
169	F	<i>t</i> -butyl	OMe		U, E	(M+H) ⁺ 514 <i>t</i> _R 1.94 min. ^c
170	H	<i>t</i> -butyl	Me		N, E	(M+H) ⁺ 436 <i>t</i> _R 1.79 min. ^c

171	H	<i>t</i> -butyl	H		V, F	(M+H) ⁺ 408 <i>t</i> _R 1.36 min. ^c
172	F	<i>t</i> -butyl	H		V, F	(M+H) ⁺ 426 <i>t</i> _R 1.75 min. ^c
173	H	<i>t</i> -butyl	OMe		V, F	(M+H) ⁺ 438 <i>t</i> _R 1.58 min. ^c
174	F	<i>t</i> -butyl	OMe		V, F	(M+H) ⁺ 456 <i>t</i> _R 1.70 min. ^c
175	H	<i>t</i> -butyl	H		V, F	(M+H) ⁺ 421 <i>t</i> _R 1.59 min. ^c
176	F	<i>t</i> -butyl	H		V, F	(M+H) ⁺ 439 <i>t</i> _R 1.71 min. ^c
177	H	<i>t</i> -butyl	OMe		V, F	(M+H) ⁺ 451 <i>t</i> _R 1.44 min. ^c
178	F	<i>t</i> -butyl	OMe		V, F	(M+H) ⁺ 469 <i>t</i> _R 1.51 min. ^c
179	F	<i>t</i> -butyl	OMe		N, E	(M+H) ⁺ 470 <i>t</i> _R 1.76 min. ^c

180	F	<i>t</i> -butyl	OMe		N, E	(M+H) ⁺ 484 <i>t</i> _R 1.70 min. ^c
181	H	<i>t</i> -butyl	OMe		N, E	(M+H) ⁺ 466 <i>t</i> _R 1.70 min. ^c
182	F	<i>t</i> -butyl	H		W, J, E	(M+H) ⁺ 469 <i>R</i> _f = 0.31 (94/6 CH ₂ Cl ₂ /MeOH)
183	H	<i>t</i> -butyl	H		W, J, E	(M+H) ⁺ 449 <i>R</i> _f = 0.27 (94/6 CH ₂ Cl ₂ /MeOH)
184	F	<i>t</i> -butyl	H		W, J, E	(M+H) ⁺ 467 <i>R</i> _f = 0.40 (94/6 CH ₂ Cl ₂ /MeOH)
185	H	<i>t</i> -butyl	H		W, J, E	(M+H) ⁺ 437 <i>R</i> _f = 0.25 (95/5 CH ₂ Cl ₂ /MeOH)
186	F	<i>t</i> -butyl	H		W, J, E	(M+H) ⁺ 455 <i>R</i> _f = 0.35 (95/5 CH ₂ Cl ₂ /MeOH)
187	H	<i>t</i> -butyl	H		W, J, E	(M+H) ⁺ 435 <i>R</i> _f = 0.35 (92/8 CH ₂ Cl ₂ /MeOH)
188	F	<i>t</i> -butyl	H		W, J, E	(M+H) ⁺ 452 <i>R</i> _f = 0.22 (94/6 CH ₂ Cl ₂ /MeOH)

189	H	<i>t</i> -butyl	H		W, J, E	(M+H) ⁺ 451 <i>R_f</i> = 0.43 (92/8 CH ₂ Cl ₂ /MeOH)
190	H	<i>t</i> -butyl	H		W, J, E, X	(M+H) ⁺ 435 <i>R_f</i> = 0.11 (92/8 CH ₂ Cl ₂ /MeOH)
191	F	<i>t</i> -butyl	H		W, J, E, X	(M+H) ⁺ 453 <i>R_f</i> = 0.12 (94/6 CH ₂ Cl ₂ /MeOH)
192	H	<i>t</i> -butyl	OMe		O, E	(M+H) ⁺ 452 <i>R_f</i> = 0.11 (4/1 CH ₂ Cl ₂ /MeOH)
193	F	<i>t</i> -butyl	OMe		O, E	(M+H) ⁺ 470 <i>R_f</i> = 0.43 (85/15 CH ₂ Cl ₂ /MeOH)
194	H	<i>t</i> -butyl	H		O	(M+H) ⁺ 418 <i>R_f</i> = 0.32 (9/1 CH ₂ Cl ₂ /MeOH)
195	H	<i>t</i> -butyl	OMe		N, E	(M+H) ⁺ 466 <i>R_f</i> = 0.30 (1/9 MeOH/CH ₂ Cl ₂)
196	H	<i>t</i> -butyl	OMe		D, E	(M+H) ⁺ 468 <i>t_R</i> 1.62 min. ^b
197	F	<i>t</i> -butyl			H, D, M, E	(M+H) ⁺ 511 <i>R_f</i> = 0.21 (2/3 MeOH/EtOAc)

198	H	<i>t</i> -butyl			H, D, M, E	(M+H) ⁺ 493 <i>R_f</i> = 0.15 (2/3 MeOH/EtOAc)
199	H	<i>t</i> -butyl	CH ₃		I, K, E	(M+H) ⁺ 480 <i>R_f</i> = 0.55 (79/20/1 CH ₃ CN/MeOH/H ₂ O)
200	F	<i>t</i> -butyl	CH ₃		I, K, E	(M+H) ⁺ 498 <i>R_f</i> = 0.75 (79/20/1 CH ₃ CN/MeOH/H ₂ O)
201	H	<i>t</i> -butyl	CH ₃		I, K, E	(M+H) ⁺ 466 <i>R_f</i> = 0.18 (79/20/1 CH ₃ CN/MeOH/H ₂ O)
202	H	<i>t</i> -butyl	CH ₃		I, K, F	(M+H) ⁺ 500 <i>R_f</i> = 0.65 (79/20/1 CH ₃ CN/MeOH/H ₂ O)
203	F	<i>t</i> -butyl	CH ₃		I, K, E	(M+H) ⁺ 484 <i>R_f</i> = 0.22 (79/20/1 CH ₃ CN/MeOH/H ₂ O)
204	F	<i>t</i> -butyl	CH ₃		I, K, F	(M+H) ⁺ 518 <i>R_f</i> = 0.71 (79/20/1 CH ₃ CN/MeOH/H ₂ O)
205	H	<i>t</i> -butyl	CH ₃		I, K, E	(M+H) ⁺ 480 <i>R_f</i> = 0.53 (79/20/1 CH ₃ CN/MeOH/H ₂ O)
206	F	<i>t</i> -butyl	CH ₃		I, K, E	(M+H) ⁺ 498 <i>R_f</i> = 0.70 (79/20/1 CH ₃ CN/MeOH/H ₂ O)

207	F		CH ₃		I, K, E	(M+H) ⁺ 506 <i>R_f</i> = 0.45 (79/20/1 CH ₃ CN/MeOH/H ₂ O)
208	F		CH ₃		I, K, E	(M+H) ⁺ 482 <i>R_f</i> = 0.45 (49/50/1 CH ₃ CN/MeOH/H ₂ O)
209	F		CH ₃		I, K, F	(M+H) ⁺ 516 <i>R_f</i> = 0.72 (79/20/1 CH ₃ CN/MeOH/H ₂ O)
210	F		CH ₃		I, K, E	(M+H) ⁺ 496 <i>R_f</i> = 0.41 (100% EtOAc)
211	F		CH ₃		I, K, E	(M+H) ⁺ 496 <i>R_f</i> = 0.25 (100% EtOAc)

^aThe structures of the final compounds were confirmed by ¹H NMR spectroscopy and the spectra were consistent with the desired chemical structures.

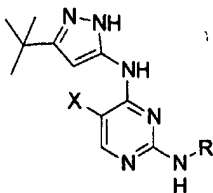
^bAnalytical HPLC were obtained using a Gilson HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (50 x 4.6 mm, 12μm).

- 5 The eluents were A: acetonitrile w/0.1% TFA and B: H₂O w/0.1% TFA. Gradient elution from 10% B to 90% over 4 min at a flowrate of 4.0 mL/min was used with an initial hold of 0.5 min and a final hold at 90% B of 0.5 minutes. Total run time was 5 min.

- ^cHPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm,
10 a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flowrate of 1.0 mL/min was used

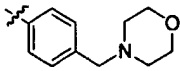
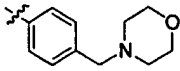
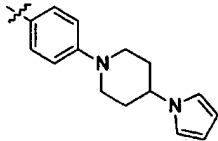
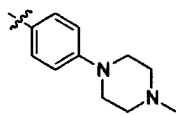
with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Table 2. Other Compounds Prepared by general method C.



5

Example	X	R	Preparation of Aniline Sidechain	Characterization ^a
212	F		D, E	(M+H) ⁺ 456 <i>t_R</i> 1.62 min. ^b
213	CH ₃		D, E	(M+H) ⁺ 438 <i>t_R</i> 1.70 min. ^b
214	H		D, E	(M+H) ⁺ 438 <i>t_R</i> 1.63 min. ^b
215	H		D, E	(M+H) ⁺ 475 <i>t_R</i> 1.61 min. ^b
216	Br		D, E	(M+H) ⁺ 502 <i>t_R</i> 1.83 min. ^b

217	H		V, F	(M+H) ⁺ 408 <i>t_R</i> 1.09 min. ^c
218	F		V, F	(M+H) ⁺ 426 <i>t_R</i> 1.72 min. ^c
219	H		Commercial (Maybridge)	(M+H) ⁺ 457 <i>R_f</i> = 0.20 (4/1 EtOAc/Hex)
220	H		Commercial (Bionet)	(M+H) ⁺ 407 <i>R_f</i> = 0.23 (4/1 EtOAc/Hex)

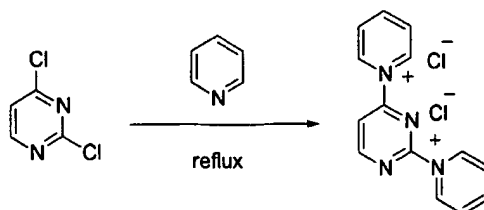
^aThe structures of the final compounds were confirmed by ¹H NMR spectroscopy and the spectra were consistent with the desired chemical structures.

^bAnalytical HPLC were obtained using a Gilson HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (50 x 4.6 mm, 12μm).

5 The eluents were A: acetonitrile w/0.1% TFA and B: H₂O w/0.1% TFA. Gradient elution from 10% B to 90% over 4 min at a flowrate of 4.0 mL/min was used with an initial hold of 0.5 min and a final hold at 90% B of 0.5 minutes. Total run time was 5 min.\

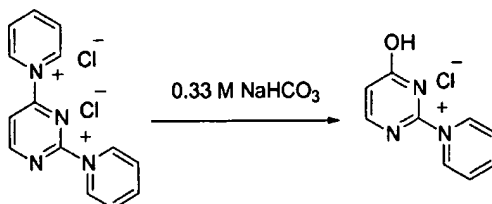
^cHPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm,
10 a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flowrate of 1.0 mL/min was used
15 with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Method Y. Preparation of 1-[2-(1-pyridiniumyl)-4-pyrimidinyl]pyridinium dichloride



A solution of 2,4-dichloropyrimidine (84.6 g, 567.9 mmol) in anhydrous pyridine (2.5 L) was heated slowly to reflux over 2 h with mechanical stirring and kept at reflux for 10 min. Over the course of the reaction, a thick precipitate formed which became pink in color. The reaction was cooled to rt over 24 h, then the solid filtered through a coarse sintered glass funnel. The cake washed with copious amounts of ether then dried in vacuo to give the desired product as a light purple / brown fluffy solid in 99% yield (173.3 g, 564.2 mmol). ¹H NMR (DMSO) δ 10.33 (2H, d, J = 6.9 Hz), 10.18 (2H, d, J = 7.2 Hz), 9.78 (1H, d, J = 5.1 Hz), 9.07 and 9.02 (2H, t overlapping, J = 6.0 and 7.8 Hz), 8.95 (1H, d, J = 5.4 Hz), 8.49 (4H, m).

Method Z. Preparation of 1-(4-hydroxy-2-pyrimidinyl)pyridinium chloride



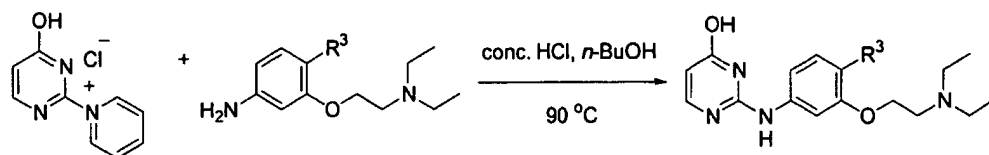
A solution of 1-[2-(1-pyridiniumyl)-4-pyrimidinyl]pyridinium dichloride (100 g, 325.5 mmol) in 0.33 M NaHCO₃ solution (109.4 g NaHCO₃ in 3.91 L dH₂O) was stirred at 23 °C for 24 h. The brown solution slowly evolved CO₂ (final reaction pH after this time = 7-7.5). The reaction was concentrated by rotary evaporation at 6 mm vacuum at 30 °C and the crude brown sludge (still containing water) suspended in methanol and coated on silica gel (700 ml) by concentration in vacuo. The silica-coated crude was then purified on a plug of silica gel (1 L), eluting with a gradient of 100% CH₃CN (2 L) → 5% MeOH/CH₃CN (1 L) → 10% MeOH/CH₃CN (1 L) → 20% MeOH/CH₃CN (6 L) → 50% MeOH/CH₃CN (1 L) → 50%

MeOH/CH₃CN (2 L). The fractions containing product were pooled and concentrated in vacuo to give a brown solid. This was triturated in MeOH (700 ml) with water (300 ml) and the insoluble salts filtered off and washed with MeOH. The filtrate was again coated on silica gel (300 ml) and the column purification repeated as above to give an amber oil/solid.

5 This was again suspended in MeOH/water (2:1) and concentrated until a precipitate formed. The salts were again filtered off and washed with CH₃CN and acetone. The filtrate was concentrated in vacuo to a brown gum which solidified after drying in vacuo under P₂O₅. The solid was pulverized with a mortar and pestle then suspended in acetone (1 L), sonicated, and filtered washing with acetone. The desired product was obtained as a light tan
10 solid in 65% yield (44.04 g, 210.1 mmol) after drying in vacuo under P₂O₅ for 24 h. TLC: *R_f* = 0.40 (33% methanol/dichloromethane); *R_f* = 0.20 (33% methanol/acetonitrile with 1% water); MS (ESI-MS): 174 (M+H)⁺; *t_R* 0.74 min.; ¹H NMR (DMSO) δ 9.89 (2H, d, *J* = 6.9 Hz), 8.84 (1H, t, *J* = 7.5 Hz), 8.41 (1H, d, *J* = 5.7 Hz), 8.29 (2H, t, *J* = 7.2 Hz), 6.79 (1H, d, *J* = 6.0 Hz).

15

General Method AA. Preparation of substituted 2-({3-[2-(diethylamino)ethoxy]phenyl}amino)-4-pyrimidinols



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2-({3-[2-(diethylamino)ethoxy]phenyl}amino)-4-pyrimidinol (*R*³ = H)

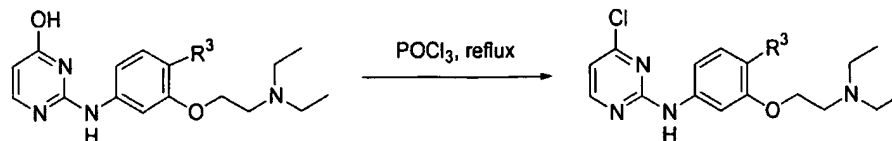
A suspension of 1-(4-hydroxy-2-pyrimidinyl)pyridinium chloride (14.19 g, 67.69 mmol) and 3-[2-(diethylamino)ethoxy]aniline (14.10 g, 67.69 mmol) in anhydrous *n*-BuOH (600 ml) was stirred under argon. To this was added conc. HCl (16.92 ml, 203.1 mmol, 3 eq) and the brown
25 suspension stirred at 90 °C (internal temp.) for 1 h (solids dissolve). More 1-(4-hydroxy-2-pyrimidinyl)pyridinium chloride (14.19 g, 67.69 mmol) was then added followed by *n*-BuOH (150 ml). The brown solution was stirred at 90 °C (internal temp.) for 16 h. A white ppt formed in the reaction. The solvent was removed by rotary evaporation at 2 mm vacuum and 30 °C, and the oily residue dried in vacuo. The crude product was quenched with sat. K₂CO₃
30 (300 ml) and immediately extracted with EtOAc (2 X 1L) (note: a white ppt formed in the

biphase – this may be excess starting aniline). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give a brown gum. This was purified by silica gel chromatography (flush column) (800 ml silica gel, eluting with a gradient of 100% dichloromethane \rightarrow 50% methanol / dichloromethane (streaks off). Fractions containing
 5 product were pooled and concentrated in vacuo to give the desired product as a solid amber foam (after drying in vacuo) in 79% yield (16.20 g, 53.58 mmol). TLC: R_f = 0.25 (33% methanol / dichloromethane), R_f = 0.05 (25% water / acetonitrile); MS (ESI-MS): 303 ($\text{M}+\text{H}$)⁺; t_R 0.71 min.; ^1H NMR (DMSO) δ 9.49 (1H, vbs), 7.76 (1H, d, J = 6.6 Hz), 7.42 (1H, s), 7.18 (1H, t, J = 8.4 Hz), 7.13 (1H, d, J = 8.4 Hz), 6.58 (1H, d, J = 9.0 Hz), 5.80 (1H, d, J = 6.3 Hz),
 10 4.01 (2H, t, J = 6.3 Hz), 2.84 (2H, t, J = 6.0 Hz), 2.61 (4H, quart, J = 7.2 Hz), 1.00 (6H, t, J = 6.9 Hz).

2-({3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}amino)-4-pyrimidinol ($\text{R}^3 = \text{OCH}_3$)

The general procedure used in the preparation of 2-({3-[2-(diethylamino)ethoxy]phenyl}amino)-4-pyrimidinol ($\text{R} = \text{H}$) was also used in the preparation of
 15 2-({3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}amino)-4-pyrimidinol ($\text{R} = \text{OCH}_3$) using 1-(4-hydroxy-2-pyrimidinyl)pyridinium chloride (32.50 g, 153.46 mmol), 3-[2-(diethylamino)ethoxy]-4-methoxyaniline (35.00 g, 139.51 mmol), and conc. HCl (34.9 ml, 418.5 mmol) in anhydrous $n\text{-BuOH}$ (500 ml). Product was obtained as a solid amber foam in
 20 40% yield (18.99 g, 57.13 mmol). TLC: R_f = 0.15 (50/49/1 methanol/acetonitrile/water); MS (ESI-MS): 333 ($\text{M}+\text{H}$)⁺; t_R = 0.75 min.; ^1H NMR (CD_3OD) δ 7.62 (1H, d, J = 6.3 Hz), 7.25 (1H, d, J = 2.4 Hz), 6.95 (2H, m), 5.81 (1H, d, J = 6.6 Hz), 4.15 (2H, t, J = 5.7 Hz), 3.81 (3H, s), 3.02 (2H, t, J = 5.7 Hz), 2.78 (4H, quart, J = 7.5 Hz), 1.13 (6H, t, J = 6.9 Hz).

25 General Method AB. Preparation of substituted 4-chloro-*N*-{3-[2-(diethylamino)ethoxy]phenyl}-2-pyrimidin-amines



30 4-chloro-*N*-{3-[2-(diethylamino)ethoxy]phenyl}-2-pyrimidinamine ($\text{R}^3 = \text{H}$)

A suspension of 2-({3-[2-(diethylamino)ethoxy]phenyl}amino)-4-pyrimidinol (5.40 g, 17.86 mmol, R = H) in phosphorous oxychloride (200 ml) was heated to reflux (solid dissolves) and the POCl₃ distilled off over 1h to give a concentrated reaction volume of 50 ml POCl₃. The dark brown solution was quenched by dropwise addition to ice water (mostly ice) (1.5 L) with vigorous stirring over 15 min. (note: the secondary container also contained ice). The internal temp. was kept at <5 °C during the quench. This was stirred from 0 °C → rt over 20 h with vigorous stirring. The acidic solution was then cooled to 0 °C with an ice bath, and quenched by portionwise addition of powdered K₂CO₃ (380 g) over 1.5 h with vigorous stirring to a final pH of 11.5 (internal temp. always kept at <8 °C during the quench; vigorous bubbling observed). The still-cold light brown solution is extracted with EtOAc (2L), and this was dried (Na₂SO₄), filtered, and concentrated in vacuo to give an amber oil. This was purified by a silica gel plug (flush column) (200 ml silica gel, eluting with a gradient of 100% acetonitrile → 50% water/acetonitrile). Fractions containing product were pooled and concentrated in vacuo to give an amber oil. This crystallized to an amber solid over 48 h of drying in vacuo to give the desired product in 77% yield (4.18 g, 13.03 mmol). TLC: *R_f* = 0.20 (25% water/acetonitrile); MS (ESI-MS): 321 (M+H)⁺; *t_R* = 1.97 min.; ¹H NMR (DMSO) δ 9.99 (1H, s), 8.42 (1H, d, *J* = 5.4 Hz), 7.39 (1H, s), 7.16 (1H, t, *J* = 8.1 Hz), 7.23 (1H, d, *J* = 8.4 Hz), 6.94 (1H, d, *J* = 4.8 Hz), 5.56 (1H, d, *J* = 7.8 Hz), 3.98 (2H, t, *J* = 5.7 Hz), 2.80 (2H, b s), 2.47 (4H, b s), 0.97 (6H, t, *J* = 7.2 Hz).

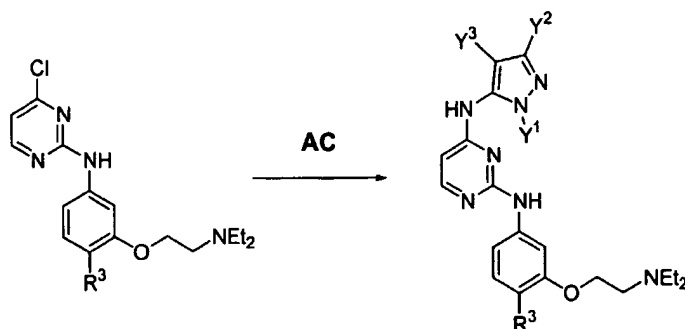
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4-chloro-*N*-{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2-pyrimidinamine (R³ = OCH₃)

The general procedure used in the preparation of the above 4-chloro-*N*-{3-[2-(diethylamino)ethoxy]phenyl}-2-pyrimidin-amine was also used in the preparation of compound 4-chloro-*N*-{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2-pyrimidinamine using 2-({3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}amino)-4-pyrimidinol (12.27 g, 35.81 mmol) in phosphorous oxychloride (250 ml), except the reaction was stirred at ambient temp for 20 h instead of being refluxed. The product was obtained as a brown oil which crystallized to a brown in 86% yield (11.10 g, 31.64 mmol). TLC: *R_f* = 0.35 (50/49/1 methanol/acetonitrile/water); MS (ESI-MS): 351/353 (M+H)⁺; *t_R* = 1.83 min.; ¹H NMR (CD₃OD) δ 8.25 (1H, d, *J* = 5.4 Hz), 7.42 (1H, d, *J* = 2.7 Hz), 7.13 (1H, dd, *J* = 2.4, 8.7 Hz), 6.90 (1H, d, *J* = 8.7 Hz), 6.76 (1H, d, *J* = 5.4 Hz), 4.14 (2H, t, *J* = 5.7 Hz), 3.81 (3H, s), 2.97 (2H, t, *J* = 5.7 Hz), 2.73 (4H, quart, *J* = 7.5 Hz), 1.11 (6H, t, *J* = 6.9 Hz).

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General Method AC. Coupling of 5-amino-3-substituted pyrazoles with substituted 4-chloro-*N*-{3-[2-(diethylamino)ethoxy]phenyl}-2-pyrimidin-amines using dilute conditions



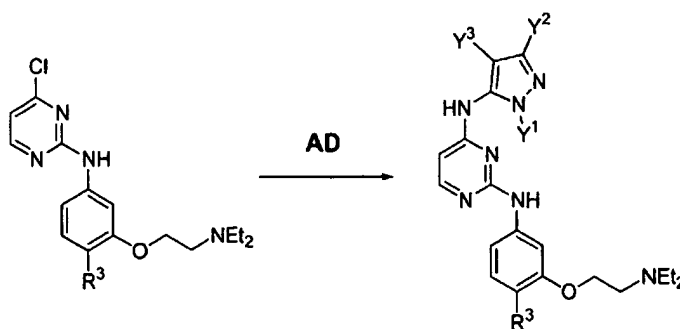
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4-Chloropyrimidine intermediate (1 equiv), aminopyrazole (1.25 equiv), *n*-BuOH (0.15 M), and HCl (conc., 1 drop) are combined and heated at 100 °C overnight. The mixture is taken up in CH₂Cl₂ and washed with NaHCO₃ before being dried (Na₂SO₄) and concentrated.

10 Purification of the residue by flash silica gel chromatography provides the desired 2,4-diaminopyrimidines whose structures are confirmed by LC/MS and ¹H NMR.

General Method AD. Coupling of 5-amino-3-substituted pyrazoles with substituted 4-chloro-*N*-{3-[2-(diethylamino)ethoxy]phenyl}-2-pyrimidin-amines using concentrated conditions

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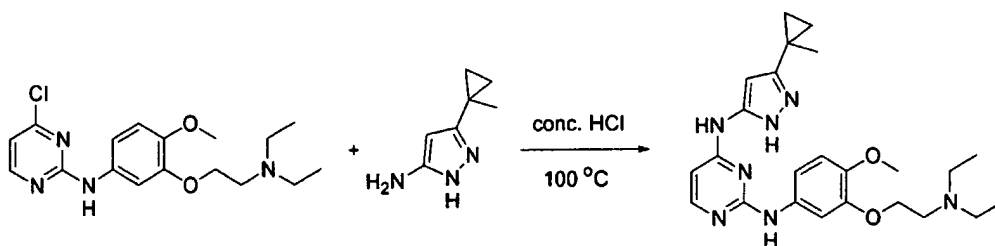
4-Chloropyrimidine intermediate (1 equiv), aminopyrazole (1.25 equiv), and HCl (conc., 1 drop) are combined and melted at 100 °C overnight. The mixture is taken up in CH₂Cl₂ and washed with NaHCO₃ before being dried (MgSO₄) and concentrated. Purification of the residue by flash silica gel chromatography or preparative HPLC provides the desired 2,4-

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diaminopyrimidienes whose structures are confirmed by LC/MS and ^1H NMR.

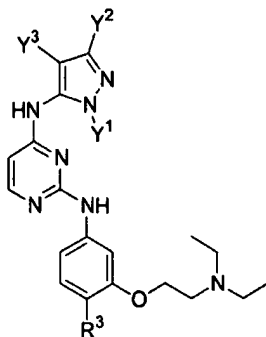
Example 221: N^2 -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- N^4 -[3-(1-methylcyclopropyl)-1H-pyrazol-5-yl]-2,4-pyrimidinediamine




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

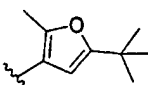

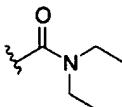
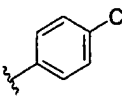




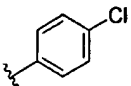
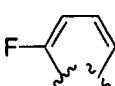

To a homogenized mixture of 4-chloro- N -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}-2-pyrimidinamine (100 mg, 0.280 mmol) and 5-amino-3-(1-methylcyclopropyl)-1H-pyrazole (117
 10 mg, 0.830 mmol) was added conc. HCl (0.048 ml, 0.576 mmol) and the vial sealed and melted to an amber oil at 100 °C for 1 h. The reaction was cooled, dissolved in MeOH (10 ml), quenched with sat. K_2CO_3 (50 ml), and extracted with EtOAc (2 X 150 ml). The combined organics were dried (Na_2SO_4) and the solvent removed in vacuo. The crude product was purified by silica gel chromatography (100% acetonitrile \rightarrow 5% water/methanol gradient). The
 15 fractions containing product were concentrated in vacuo, and the residue dissolved in dichloromethane and filtered to remove silica gel. Hexane was added, and the solvent removed in vacuo to give a solid. The product was isolated as a light pink solid from hexane in 68% yield (88 mg, 0.195 mmol). TLC: R_f = 0.20 (50/49/1 methanol/acetonitrile/water); MS (ESI-MS): 452 ($\text{M}+\text{H}$) $^+$; t_R = 1.60 min.; ^1H NMR (CD_3OD) δ 7.89 (1H, bs), 7.25 (1H, bs), 7.05 (1H,
 20 dd, J = 2.4, 8.7 Hz), 6.92 (1H, d, J = 9.0 Hz), 6.22 (2H, bs), 4.09 (2H, t, J = 6.3 Hz), 3.82 (3H, s), 2.94 (2H, t, J = 5.4 Hz), 2.69 (4H, quart, J = 6.9 Hz), 1.38 (3H, s), 1.09 (6H, t, J = 7.5 Hz), 0.87 (2H, bs), 0.74 (2H, bs).

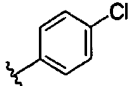
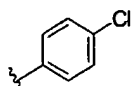
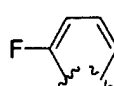
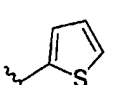
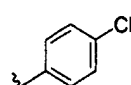
The compounds of examples 220-258 are prepared by general method AC or AD
 25 where a 4-chloropyrimidine (prepared by methods Y-AB) is reacted with an amino pyrazole (prepared by general method A):

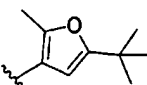
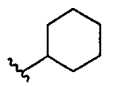
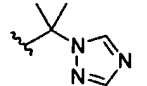
Table 3. Compounds Prepared by general methods AC or AD

Example	Y ¹	Y ²	Y ³	R ³	Method	Characterization ^a
222	H	CF ₃	H	H	AD	(M+H) ⁺ 436 <i>R_f</i> = 0.20 (5/1 CH ₂ Cl ₂ /MeOH)
223	H	CF ₃	H	OMe	AD	(M+H) ⁺ 466 <i>R_f</i> = 0.19 (5/1 CH ₂ Cl ₂ /MeOH)
224	H		H	H	AD	(M+H) ⁺ 438 <i>R_f</i> = 0.22 (5/1 CH ₂ Cl ₂ /MeOH)
225	H		H	OMe	AD	(M+H) ⁺ 468 <i>t_R</i> 1.87 min. ^b
226	CH ₃	CH ₃	H	H	AD ^c	(M+H) ⁺ 396 <i>R_f</i> = 0.34 (9/1 CH ₂ Cl ₂ /MeOH)
227	H		H	H	AD	(M+H) ⁺ 408 <i>t_R</i> 1.58 min. ^b

228	H		H	OMe	AD	(M+H) ⁺ 438 <i>t_R</i> 1.54 min. ^b
229	H		H	H	AD	(M+H) ⁺ 436 <i>R_f</i> = 0.21 (9/1 CH ₂ Cl ₂ /MeOH)
230	H		H	OMe	AD	(M+H) ⁺ 466 <i>R_f</i> = 0.20 (9/1 CH ₂ Cl ₂ /MeOH)
231	H	adamantyl	H	H	AD	(M+H) ⁺ 502 <i>t_R</i> 2.17 min. ^b
232	H	adamantyl	H	OMe	AD	(M+H) ⁺ 532 <i>t_R</i> 2.09 min. ^b
233	H		H	H	AD ^c	(M+H) ⁺ 504 <i>t_R</i> 2.12 min. ^b
234	H		H	H	AD ^c	(M+H) ⁺ 434 <i>t_R</i> 1.65 min. ^b
235	H		H	OMe	AD ^d	(M+H) ⁺ 497 <i>t_R</i> 1.68 min. ^b
236	H		CN	H	AD ^c	(M+H) ⁺ 504 <i>t_R</i> 2.00 min. ^b

237	CH ₃		H	H	AD ^c	(M+H) ⁺ 422 <i>t</i> _R 1.56 min. ^b
238	CH ₂ CH ₃	H	H	OMe	AD ^c	(M+H) ⁺ 426 <i>t</i> _R 1.43 min. ^b
239		CH ₃	H	OMe	AD ^c	(M+H) ⁺ 487 <i>t</i> _R 1.81 min. ^b
240	Me	<i>t</i> -butyl	H	OMe	AC ^c	(M+H) ⁺ 468 <i>R</i> _f = 0.07 (8/2 CH ₂ Cl ₂ /MeOH)
241	Me		H	OMe	AC ^c	(M+H) ⁺ 522 <i>R</i> _f = 0.06 (8/2 CH ₂ Cl ₂ /MeOH)
242	H	Ph	Br	OMe	AC ^c	(M+H) ⁺ 552 <i>R</i> _f = 0.08 (8/2 CH ₂ Cl ₂ /MeOH)
243	H			OMe	AC ^c	(M+H) ⁺ 466 <i>R</i> _f = 0.08 (8/2 CH ₂ Cl ₂ /MeOH)
244	Me		H	OMe	AC ^c	(M+H) ⁺ 452 <i>R</i> _f = 0.05 (8/2 CH ₂ Cl ₂ /MeOH)
245	H	H	H	H	AC ^c	(M+H) ⁺ 368 <i>R</i> _f = 0.03 (9/1 CH ₂ Cl ₂ /MeOH)

246	H	Me	H	H	AC ^c	(M+H) ⁺ 382 $R_f = 0.04$ (9/1 CH ₂ Cl ₂ /MeOH)
247	H		H	H	AC ^c	(M+H) ⁺ 478 $R_f = 0.19$ (8/2 CH ₂ Cl ₂ /MeOH)
248	H	H	H	OMe	AC ^c	(M+H) ⁺ 398 $R_f = 0.13$ (8/2 CH ₂ Cl ₂ /MeOH)
249	H	H	CO ₂ Et	H	AD ^c	(M+H) ⁺ 440 $R_f = 0.50$ (8/2 CH ₂ Cl ₂ /MeOH)
250	H		H	OMe	AC ^c	(M+H) ⁺ 508 $R_f = 0.18$ (8/2 CH ₂ Cl ₂ /MeOH)
251	H		H	H	AC ^c	(M+H) ⁺ 436 $R_f = 0.18$ (8/2 CH ₂ Cl ₂ /MeOH)
252	H		H	H	AD ^c	(M+H) ⁺ 450 $R_f = 0.18$ (8/2 CH ₂ Cl ₂ /MeOH)
253	Me		H	H	AD ^c	(M+H) ⁺ 492 $R_f = 0.20$ (8/2 CH ₂ Cl ₂ /MeOH)
254	H	<i>p</i> -tolyl	H	H	AC ^c	(M+H) ⁺ 458 $R_f = 0.20$ (8/2 CH ₂ Cl ₂ /MeOH)

255	H		H	H	AC ^c	(M+H) ⁺ 504 <i>R_f</i> = 0.25 (8/2 CH ₂ Cl ₂ /MeOH)
256	H		H	OMe	AD	(M+H) ⁺ 480 <i>R_f</i> = 0.18 (50/49/1 MeOH/CH ₃ CN/H ₂ O)
257	CH ₃	<i>t</i> -butyl	H	H	AD ^c	(M+H) ⁺ 438 <i>R_f</i> = 0.36 (1/9 MeOH/CHCl ₃)
258	H		H	OMe	AD	(M+H) ⁺ 438 <i>R_f</i> = 0.36 (1/9 MeOH/CHCl ₃)

^aThe structures of the final compounds were confirmed by ¹H NMR spectroscopy and the spectra were consistent with the desired chemical structures.

^bAnalytical HPLC were obtained using a Gilson HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (50 x 4.6 mm, 12μm).

- 5 The eluents were A: acetonitrile w/0.1% TFA and B: H₂O w/0.1% TFA. Gradient elution from 10% B to 90% over 4 min at a flowrate of 4.0 mL/min was used with an initial hold of 0.5 min and a final hold at 90% B of 0.5 minutes. Total run time was 5 min.

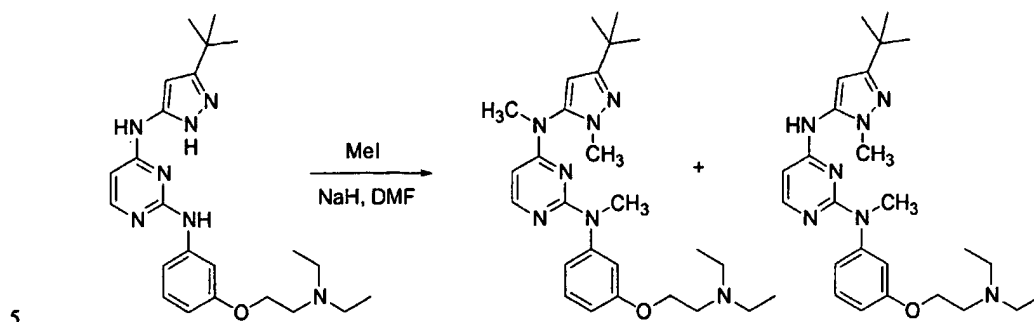
^cPyrazole is commercially available.

- ^dPyrazole was prepared as follows: To a solution of 5-nitro-1*H*-pyrazole-3-carboxylic acid (1 equiv) in THF (0.32 M) was added CDI (1 equiv). The reaction was allowed to stir for 5 min and then diethylamine (1.5 equiv) was added via syringe. The reaction mixture was stirred overnight at room temperature and concentrated. The residue was purified by preparative HPLC using 10-90%ACN/H₂O to afford the intermediate nitro pyrazole whose structure was confirmed by LC/MS and ¹H NMR.

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Example 259. Preparation of *N*⁴-(3-*tert*-butyl-1-methyl-1*H*-pyrazol-5-yl)-*N*²-{3-[2-(diethyl-amino)ethoxy]phenyl}-*N*²,*N*⁴-dimethyl-2,4-pyrimidinediamine

Example 260. N^4 -(3-*tert*-butyl-1-methyl-1H-pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]-phenyl}- N^2 -methyl-2,4-pyrimidine-diamine



To N^4 -(3-*tert*-butyl-1H-pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}-2,4-pyrimidine-diamine (75 mg, 0.17 mmol) in anhydrous *N,N*-dimethylformamide (1.8 mL) was added 60% sodium hydride in mineral oil (25 mg, 0.62 mmol, 3.5 eq). After 1h, methyl iodide (16mL, 0.26mmol, 1.5 eq) was added, and the reaction mixture was stirred at room temperature for 16h. The reaction was quenched with saturated ammonium chloride (1 mL) and poured into ethyl acetate. The organic layer was extracted with water (2 x 25 mL) and brine (1 x 25 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude organic concentrate was purified using MPLC (Biotage) eluted with 10% methanol – dichloromethane with 1% ammonium hydroxide followed by 20% methanol – dichloromethane with 1% ammonium hydroxide. The first product to elute was N^4 -(3-*tert*-butyl-1-methyl-1H-pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^2,N^4 -dimethyl-2,4-pyrimidine-diamine (10.0 mg, 12.1% yield) as a white solid; MS (ESI-MS): 466 (M+H)⁺; R_f = 0.74 (3/1 CH₂Cl₂/MeOH) followed by N^4 -(3-*tert*-butyl-1-methyl-1H-pyrazol-5-yl)- N^2 -{3-[2-(diethylamino)ethoxy]phenyl}- N^2 -methyl-2,4-pyrimidine-diamine (5.0 mg, 6.2%) as a white solid; MS (ESI-MS): 452, (M+H)⁺; R_f = 0.59 (3/1 CH₂Cl₂/MeOH).

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Assays for testing the activity of the compounds

This section describes assays that can be used to characterize compounds of the invention, e.g., src kinase activity assays; assays for testing the activity of compounds on kinases other than src; and assays for testing the activity of compounds on cell proliferation and differentiation.

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A preferred method for measuring src kinase activity (a "src biochemical assay") uses ATP (5 μ M/well) mixed with biotinylated poly-GAT substrate (10 nM/well), Streptavidin-APC (15 nM/well) and European-labeled anti-phosphotyrosine antibody (2.5 nM/well). 10 μ l of a mixture of these components is added to each well of a black 96-well plate, with or without test compound (5 μ l desired concentration of compound in DMSO). 75 μ l of assay buffer (50 mM HEPES pH 7.5, 0.1 mM EDTA, 0.015% BRIJ 35 solution, 0.1 mg/mL BSA, 0.1% beta-mercaptoethanol, 10 mM magnesium chloride) is then added to each well. Last, the src kinase (0.1 units/well) (Upstate Biotech, Lake Placid, NY) is added (10 μ l) to a final volume of 100 μ l. After 3-hour incubation at room temperature, plates are read on Wallac 1420 Victor Multilabel Counter (Perkin ElmerTM Life Sciences, Boston, MA) at 665 and 615 nm. A specific signal is the ratio of the value of the signal at 665 and the value of the signal at 615 multiplied by 10,000 (i.e., (signal at 665/signal at 615) x 10,000). Compounds that cause the specific signal to decrease inhibit the kinase activity of src. Percent inhibitions and/or IC₅₀ values can then be calculated based on specific signals from wells that have no compound added, i.e., zero percent inhibition.

A specific signal is the ratio of the value of the signal at 665 and the value of the signal at 615 multiplied by 10,000 (i.e., (signal at 665/signal at 615) x 10,000). Compounds that cause the specific signal to decrease inhibit the kinase activity of src. Percent inhibitions and/or IC₅₀ values can then be calculated based on specific signals from wells that have no compound added, i.e., zero percent inhibition.

Compounds of examples 1, 4, 6, 9-13, 15-21, 23-28, 49-52, 54-56, 58, 59, 61-63, 70, 74, 75, 78, 80-88, 90-94, 96, 98-100, 107, 111, 115, 116, 132, 136-141, 144-147, 150, 151, 153-156, 159-161, 179, 180, 183, 185, 191, 195-197, 199, 201, 203, 205-208, 210, 211, 224, 228, 237, 240, 244, and 257 demonstrate an IC₅₀ less than 150 nM in the src biochemical assay. Compounds of examples 2, 3, 5, 7, 8, 14, 22, 29-32, 34-42, 44-48, 53, 57, 60, 64-69, 71-73, 76, 77, 79, 89, 95, 97, 101-103, 106, 108-110, 112-114, 117-131, 133, 135, 142, 148, 149, 152, 157, 158, 162, 163, 165-169, 171-176, 178, 181, 182, 184, 186-190, 192-194, 198, 200, 202, 204, 209, 215, 216, 219-223, 225-227, 229-232, 234, 236, 238, 239, 241, 243, 245-248, 250-252, 254-256, and 258 exhibit an IC₅₀ greater than 150 nM but less than 1.0 μ M in the src biochemical assay. Compounds of examples 33, 43, 104, 105, 134, 143, 164, 170, 177, 212-214, 217, 218, 233, 235, 242, 249, 253, 259, and 260 show an IC₅₀ greater than 1 μ M and/or percent inhibition less than 50 but greater than 30 at 1 μ M in the src biochemical

assay.

It will be understood by a person of skill in the art that modified versions of the src biochemical assay described above can be conducted. These alternative assays can also be used to test the inhibitory activity of compounds of the invention or analogs or derivatives thereof.

The assay can also be adapted to determine the inhibitory activity of compounds towards kinases other than src kinases. For example, the src kinase enzyme in the above assay can be replaced with another kinase. When testing the inhibitory activity on kinases that are not tyrosine kinases, the antibody in the assay may also have to be replaced with an antibody that is specific for the phosphorylated residue, which has been phosphorylated by the kinase.

The effect of compounds on cell proliferation can be determined, e.g., by incubating cells with varying amounts of the compounds and counting the cells over time. Viable cells can be counted by staining the cells with a specific dye, e.g., Trypan Blue, according to methods well known in the art. Other methods include measuring the incorporation of a labeled molecule into DNA or RNA or protein of cells. For example, cell proliferation is often measured by ^3H thymidine or 5-bromodeoxyuridine incorporation assays, also well known in the art. An increase in ^3H thymidine or 5-bromodeoxyuridine incorporation in cells incubated with a test compound that is similar to that in cells non incubated with the test compound indicates that the test compound is essentially not inhibiting the proliferation of the cells. On the contrary, a lower ^3H thymidine or 5-bromodeoxyuridine incorporation in cells incubated with a test compound relative to cells that were not treated with the test compound indicates that the test compound inhibits cell proliferation.

The effect of a compound on cell differentiation can be determined by visualization of the cells after having been contacted with the compound, preferably by comparison with cells which have not been contacted with the compound. The differentiation of certain cells is visible by the naked eye (e.g., that of 3T3L1 cells), whereas that of other cells may require the use of a microscope. Specific dyes can also be used to evaluate the state of differentiation of cells. Cell differentiation can also be monitored by measuring the expression level of certain genes, whose expression is known to vary during differentiation of the cells.

The effect of a compound on a cell can be determined in a cell that contains an abnormal kinase, e.g., a mutated kinase gene, or a cell which over-expresses a kinase. For example the cell can be a cell expressing a mutated form of a tyrosine kinase, e.g., src kinase, thereby transforming the cell. The cell can also be a cell that has an abnormal proliferation
5 which is not caused by an abnormal activity or level of a kinase. Cells that can be used for testing compounds of the invention include cell lines and primary cell cultures. Numerous cell lines that are transformed, e.g., by over-expression of a proto-oncogene, which encodes, e.g., a kinase, are available, e.g., from the American Type Culture Collection (ATCC, 10801 University Blvd., Manassas, Virginia 20110. Cell lines over-expressing a gene, e.g., a
10 kinase, can be prepared by transient, or preferably, stable transfection of cells with an expression plasmid containing the gene, according to methods well known in the art. Nucleic acids for use in transforming cells, e.g., nucleic acids encoding kinases, are also publicly available or can readily be obtained. Cell lines can also be obtained from transgenic animals, e.g., animals overexpressing a kinase or expressing a mutated kinase. For
15 example, MG 1361 is a breast carcinoma cell line obtained from the MMTV-neu transgenic mouse (Sacco *et al.*, Breast Cancer Res. Treat., 47:171-180 (1998)). Primary cell cultures can be established from biopsies obtained from patients, e.g., patients having cancer.

The present invention also provides methods of testing a compound (e.g., the candidate drug) for its inhibition of src, its antiproliferative effect, its effect on cell
20 differentiation and/or its toxicity on normal or wild-type cells in animals, e.g., transgenic animals, e.g., mice. Transgenic mice are produced that express a transforming agent (e.g., a growth factor receptor) under the control of a promoter, e.g., a tissue specific promoter. Such mice develop carcinomas that have genetic and pathological features that closely resemble human cancers. For example, mice expressing viral polyoma middle T antigen
25 under the control of the MMTV promoter produces highly metastatic mammary tumors with elevated c-src kinase activity (Guy *et al.* (1994) Genes and Dev. 8:23). Nude mice in which tumor cell lines have been administered can also be used. For example, breast cancer cell lines over-expressing c-src can be administered to nude mice (*see, e.g.*, Biscardi *et al.* (1998) Mol. Carcinog. 21: 261). The ability of the compound to inhibit tumor formation or growth
30 is then ascertained. In one embodiment the size of the tumor is monitored by determining the tumor size and/or weight. The compounds can be administered by a variety of ways including orally, subcutaneously, or intraperitoneally. Generally, at least two groups of

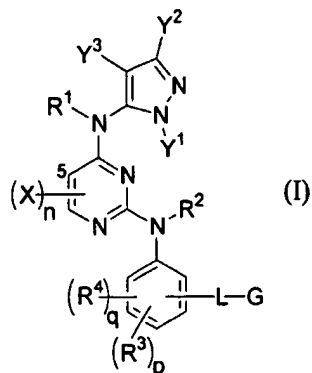
animals are used in the assay, with at least one group being a control group which is administered the administration vehicle without the compound.

An animal model for osteoporosis that can be used for testing the activity of compounds is described, e.g., in Missbach *et al.* (1999) Bone 24:437 and in Sims *et al.* (1999) J. Bone Miner. Res. 14: S183.

Other embodiments of the invention will be apparent to the skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims.

We claim

1. A compound of formula (I)



5 wherein

Y^1 represents H, C_{1-4} alkyl, or phenyl optionally substituted up to three times by
halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

Y^2 and Y^3 are independently selected from

H,

10 C_{1-6} alkyl,

C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl,

phenyl optionally substituted up to three times by halogen, C_{1-4} alkyl, or
 C_{1-4} alkoxy,

adamantyl,

15 CF_3 ,

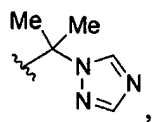
a 5-6 membered heteroaromatic containing up to two heteroatoms selected
from N, O, and S, and optionally substituted up to two times by
halogen or C_{1-6} alkyl,

$C(O)N(C_{1-4} \text{ alkyl})_2$,

20 $C(O)O(C_{1-4} \text{ alkyl})$,

CN,

halogen, and



or

Y^2 and Y^3 are joined and together represent a fused aromatic ring optionally substituted up to two times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy,

X represents halogen or C_{1-4} alkyl;

n represents 0, 1, or 2;

5 R^1 represents H or C_{1-4} alkyl;

R^2 represents H or C_{1-4} alkyl;

R^3 represents

C_{1-6} alkyl,

halogen,

10 C_{1-4} alkoxy,

O-phenyl optionally substituted up to two times by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, or di- $(C_{1-4}$ alkyl)amino,

CN, or

15 $N(R^1)_2$ wherein the R^1 moieties are independent, or the R^1 moieties optionally are joined by a linker selected from the group consisting of $CH(R^1)$, $N(R^1)$, S, $S(O)$, $S(O)_2$, and O, and taken together with the N to which they are attached, form a 5-6 membered nonaromatic heterocycle;

p represents 0, 1, or 2;

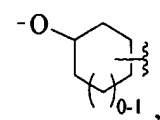
R^4 represents C_{1-4} alkyl or halogen;

20 q represents 0, 1, or 2; or

R^3 and R^4 may be joined and taken together with the carbon atoms to which they are attached, form a 5-6 membered heteroaromatic ring containing up to two heteroatoms selected from N, O, and S, and which is optionally substituted up to two times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy,

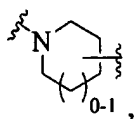
25 L is a linker selected from

$-O-(CH_2)_{1-4}-$,



$-S(O)_{0-2}-(CH_2)_{1-4}-$,

$-N(R^1)-(CH_2)_{1-4}-$,



-(CH₂)₁₋₄-O-(CH₂)₁₋₄- ,

-(CH₂)₁₋₄- ,

-C≡C-(CH₂)₁₋₄- , and

5 -N(R¹)-C(O)-(CH₂)₁₋₄- , and

G represents

NR⁵R⁶ ,

wherein

R⁵ represents H, C₁₋₆ alkyl, or C₁₋₄ alkoxy-C₁₋₄ alkyl; and

10 R⁶ represents

H,

C₁₋₆ alkyl,



C₁₋₄ alkoxy-substituted C₁₋₄ alkyl,

15 C₃₋₆ cycloalkyl optionally substituted up to 2 times by
halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy,

C₃₋₆ cycloalkyl-substituted C₁₋₄ alkyl,


benzyl,

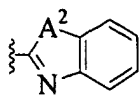
phenyl optionally substituted by halogen, C₁₋₄ alkyl,
C₁₋₄ alkoxy, -CO₂R¹, -C(O)N(R¹)₂ , -N(R¹)₂ , or by a

20 bivalent group  , or  wherein

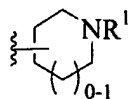
A is N(R¹), S, S(O), S(O)₂, or O , and

said bivalent group is connected to the phenyl
ring at adjacent carbon atoms to form a
fused 5-membered heterocycle,

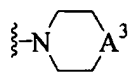
25 -(C₁₋₄ alkyl)-N  , wherein A¹ represents N(R¹), S, S(O),
S(O)₂ , or O, or



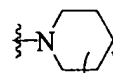
, wherein A^2 represents $N(R^1)$, S, S(O), S(O)₂, or O,



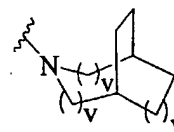
, optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl,



5, optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, and wherein A^3 represents $N(R^1)$, S, S(O), S(O)₂, or O,



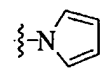
10, optionally substituted up to 2 times by oxo, (C₁₋₃ alkoxy)-(C₁₋₃ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, or up to 4 times by C₁₋₃ alkyl,



optionally substituted up to 2 times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy, and wherein

v is 0 or 1,

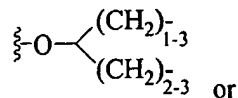
and



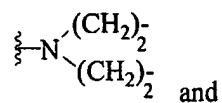
15, optionally substituted up to 2 times by C₁₋₄ alkyl,

or

L represents

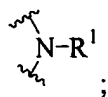


20



and

G represents



or a pharmaceutically acceptable salt thereof.

5

2. A compound of claim 1 wherein

Y¹ represents H or C₁₋₄ alkyl.

3. A compound of claim 1 wherein

10 Y¹ represents H.

4. A compound of claim 1 wherein

Y² is selected from

C₁₋₆ alkyl,

15

C₃₋₆ cycloalkyl optionally substituted by C₁₋₄ alkyl,

phenyl optionally substituted up to three times by halogen, C₁₋₄ alkyl, or

C₁₋₄ alkoxy,

adamantyl,

CF₃,

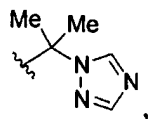
20

a 5-6 membered heteroaromatic containing up to two heteroatoms selected

from N, O, and S, and optionally substituted up to two times by

halogen or C₁₋₆ alkyl,

and



25

and Y³ is H;

or

Y² and Y³ are joined and together represent a fused aromatic ring optionally substituted up to two times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy.

5. A compound of claim 1 wherein
Y² is selected from
- 5 C₁₋₆ alkyl,
C₃₋₆ cycloalkyl optionally substituted by C₁₋₄ alkyl,
phenyl optionally substituted up to three times by halogen, C₁₋₄ alkyl, or
C₁₋₄ alkoxy,
adamantyl, and
- 10 a 5-6 membered heteroaromatic containing up to two heteroatoms selected
from N, O, and S, and optionally substituted up to two times by
halogen or C₁₋₆ alkyl,
and Y³ is H.
- 15 6. A compound of claim 1 wherein
Y² is selected from
C₁₋₆ alkyl, and
C₃₋₆ cycloalkyl optionally substituted by C₁₋₄ alkyl, and
Y³ is H.
- 20 7. A compound of claim 1 wherein
X represents Cl, F, or C₁₋₄ alkyl; and
n represents 0, 1, or 2.
- 25 8. A compound of claim 1 wherein
X represents F; and
n represents 0 or 1.
9. A compound of claim 1 wherein
30 R¹ represents H and

R^2 represents H.

10. A compound of claim 1 wherein

R^3 represents

- 5 C_{1-6} alkyl,
 halogen,
 C_{1-4} alkoxy,
 CN, or
 $N(R^1)_2$ wherein the R^1 moieties are independent, or the R^1 moieties optionally
10 are joined by a linker selected from the group consisting of $CH(R^1)$,
 $N(R^1)$, S, S(O), S(O)₂, and O, and taken together with the N to which
 they are attached, form a 5-6 membered nonaromatic heterocycle; and
 p represents 0, 1, or 2.

15 11. A compound of claim 1 wherein

R^3 represents

- C_{1-6} alkyl,
 C_{1-4} alkoxy,
 CN, or
20 $N(R^1)_2$ wherein the R^1 moieties are independent, or the R^1 moieties optionally
 are joined by a linker selected from the group consisting of $CH(R^1)$,
 $N(R^1)$, S, S(O), S(O)₂, and O, and taken together with the N to which
 they are attached, form a 5-6 membered nonaromatic heterocycle; and
 p represents 0 or 1.

25

12. A compound of claim 1 wherein

R^3 represents

- C_{1-6} alkyl,
 C_{1-4} alkoxy, or
30 $N(R^1)_2$ wherein the R^1 moieties are independent, or the R^1 moieties optionally
 are joined by a linker selected from the group consisting of $CH(R^1)$,

$N(R^1)$, S, S(O), S(O)₂, and O, and taken together with the N to which they are attached, form a 5-6 membered nonaromatic heterocycle; and p represents 0 or 1.

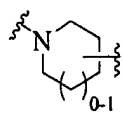
5 13. A compound of claim 1 wherein

L is selected from

-O-(CH₂)₁₋₄ ,

-S(O)₀₋₂-(CH₂)₁₋₄ ,

-N(R¹)-(CH₂)₁₋₄ ,



-(CH₂)₁₋₄-O-(CH₂)₁₋₄ ,

-(CH₂)₁₋₄ , or

-N(R¹)-C(O)-(CH₂)₁₋₄ , and

G represents

15 NR⁵R⁶ ,

wherein

R⁵ represents H or C₁₋₆ alkyl; and

R⁶ represents

C₁₋₆ alkyl,

20 C₁₋₄ alkoxy-substituted C₁₋₄ alkyl,

C₅₋₆ cycloalkyl optionally substituted up to 2 times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy,

C₃₋₆ cycloalkyl-substituted C₁₋₄ alkyl,

benzyl,

25 phenyl optionally substituted by halogen, C₁₋₄ alkyl,

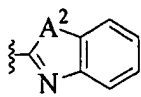
C₁₋₄ alkoxy, -CO₂R¹, -C(O)N(R¹)₂ , -N(R¹)₂ , or by a

bivalent group , or wherein

A is N(R¹), S, S(O), S(O)₂, or O , and

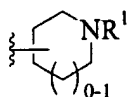
said bivalent group is connected to the phenyl ring at adjacent carbon atoms to form a fused 5-membered heterocycle,

or

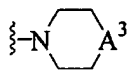


, wherein A^2 represents $N(R^1)$, S, S(O), S(O)₂, or

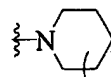
O,



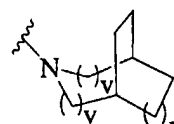
, optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ oxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl,



, optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ oxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, and wherein A³ represents N(R¹), S, S(O), S(O)₂, or O,



(¹)₀₋₁, optionally substituted up to 2 times by oxo, (C₁₋₃ alkoxy)-(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, or up to 4 times by C₁₋₃ alkyl,



v, optionally substituted up to 2 times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy, and wherein
v is 0 or 1.

14. A compound of claim 1 wherein
L is selected from

$$\begin{aligned} & -\text{O}-(\text{CH}_2)_{1-4}-, \\ & -\text{S}(\text{O})_{0-2}-(\text{CH}_2)_{1-4}-, \\ & -\text{N}(\text{R}^1)-(\text{CH}_2)_{1-4}-, \\ & -(\text{CH}_2)_{1-4}-\text{O}-(\text{CH}_2)_{1-4}-, \text{ and} \\ & -\text{N}(\text{R}^1)-\text{C}(\text{O})-(\text{CH}_2)_{1-4}-, \text{ and} \end{aligned}$$

G represents

NR^5R^6 ,

wherein

R^5 represents H or C_{1-6} alkyl; and



R^6 represents

C_{1-6} alkyl,

C_{5-6} cycloalkyl optionally substituted up to 2 times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy,

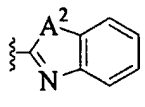
benzyl,

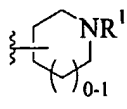
phenyl optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, $-\text{CO}_2\text{R}^1$, $-\text{C}(\text{O})\text{N}(\text{R}^1)_2$, $-\text{N}(\text{R}^1)_2$, or by a

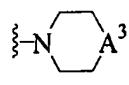
bivalent group , or  wherein

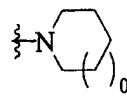
A is $\text{N}(\text{R}^1)$, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, or O, and

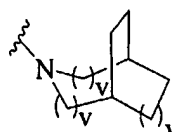
said bivalent group is connected to the phenyl ring at adjacent carbon atoms to form a fused 5-membered heterocycle, or

, wherein A^2 represents $\text{N}(\text{R}^1)$, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, or O,

₀₋₁, optionally substituted up to 2 times by C_{1-3} alkyl, $(\text{C}_{1-3}$ alkoxy)(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl,

₀₋₁, optionally substituted up to 2 times by C_{1-3} alkyl, $(\text{C}_{1-3}$ alkoxy)(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl, and wherein A^3 represents $\text{N}(\text{R}^1)$, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, or O,

₀₋₁, optionally substituted up to 2 times by oxo, $(\text{C}_{1-3}$ alkoxy)-(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl, or up to 4 times by C_{1-3} alkyl,

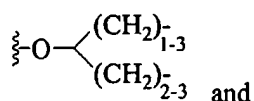


, optionally substituted up to 2 times by halogen, C₁₋₄ alkyl,
or C₁₋₄ alkoxy, and wherein
v is 0 or 1,

or

5

L represents



G represents



10

15. A compound of claim 1 wherein

L is selected from

-O-(CH₂)₁₋₄ ,
-N(R¹)-(CH₂)₁₋₄ ,
15 -(CH₂)₁₋₄-O-(CH₂)₁₋₄ , and

G represents

NR⁵R⁶ ,

wherein

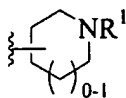
R⁵ represents H or C₁₋₆ alkyl; and

20

R⁶ represents

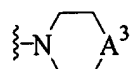
C₁₋₆ alkyl, or

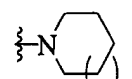
C₅₋₆ cycloalkyl optionally substituted up to 2 times by
halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy,

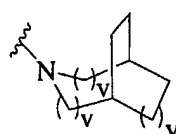


, optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃
alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl,

25

, optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, and wherein A³ represents N(R¹), S, S(O), S(O)₂, or O,

5 , optionally substituted up to 2 times by oxo, (C₁₋₃ alkoxy)-(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, or up to 4 times by C₁₋₃ alkyl,

, optionally substituted up to 2 times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy, and wherein v is 0 or 1.

10 16. A compound of claim 1 wherein

Y¹ represents H or C₁₋₄ alkyl;

Y² is selected from

C₁₋₆ alkyl,

C₃₋₆ cycloalkyl optionally substituted by C₁₋₄ alkyl,

15 phenyl optionally substituted up to three times by halogen, C₁₋₄ alkyl, or

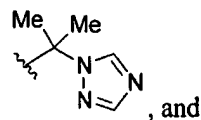
C₁₋₄ alkoxy,

adamantyl,

CF₃,

a 5-6 membered heteroaromatic containing up to two heteroatoms selected

20 from N, O, and S, and optionally substituted up to two times by halogen or C₁₋₆ alkyl, and



Y³ is H;

or

25 Y² and Y³ are joined and together represent a fused aromatic ring optionally substituted up to two times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy,

X represents Cl, F, or C₁₋₄ alkyl;

n represents 0, 1, or 2;

R¹ and R² each represents H;

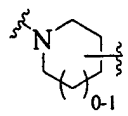
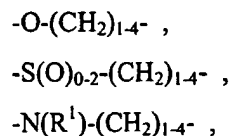
R³ represents

- 5 C₁₋₆ alkyl,
 halogen,
 C₁₋₄ alkoxy,
 CN, or
 N(R¹)₂ wherein the R¹ moieties are independent, or the R¹ moieties optionally
 10 are joined by a linker selected from the group consisting of CH(R¹),
 N(R¹), S, S(O), S(O)₂, and O, and taken together with the N to which
 they are attached, form a 5-6 membered nonaromatic heterocycle;

p represents 0, 1, or 2;

q is 0;

- 15 L is a linker selected from

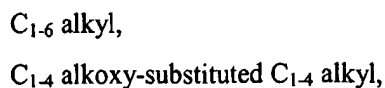


- 20 -(CH₂)₁₋₄-O-(CH₂)₁₋₄ ,
 -(CH₂)₁₋₄ , and
 -N(R¹)-C(O)-(CH₂)₁₋₄ , and

G represents



- 25 wherein
 R⁵ represents H or C₁₋₆ alkyl; and
 R⁶ represents

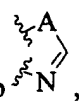



C₅₋₆ cycloalkyl optionally substituted up to 2 times by
halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy,

C₃₋₆ cycloalkyl-substituted C₁₋₄ alkyl,

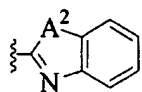
benzyl,

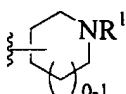
5 phenyl optionally substituted by halogen, C₁₋₄ alkyl,
C₁₋₄ alkoxy, -CO₂R¹, -C(O)N(R¹)₂, -N(R¹)₂, or by a

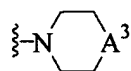
bivalent group , or  wherein

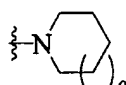
A is N(R¹), S, S(O), S(O)₂, or O, and

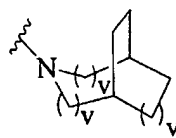
10 said bivalent group is connected to the phenyl
ring at adjacent carbon atoms to form a
fused 5-membered heterocycle, or

, wherein A² represents N(R¹), S, S(O), S(O)₂, or
O,

15 , optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃
alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl,

, optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃
alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, and
wherein A³ represents N(R¹), S, S(O), S(O)₂, or O,

20 , optionally substituted up to 2 times by oxo, (C₁₋₃ alkoxy)-(C₁₋₄
alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, or up to 4 times by
C₁₋₃ alkyl,

, optionally substituted up to 2 times by halogen, C₁₋₄ alkyl,
or C₁₋₄ alkoxy, and wherein
v is 0 or 1.

17. A compound of claim 1 wherein

Y^1 represents H;

Y^2 is selected from

- 5 C₁₋₆ alkyl,
 C₃₋₆ cycloalkyl optionally substituted by C₁₋₄ alkyl,
 phenyl optionally substituted up to three times by halogen, C₁₋₄ alkyl, or
 C₁₋₄ alkoxy,
 adamantyl,
10 a 5-6 membered heteroaromatic containing up to two heteroatoms selected
 from N, O, and S, and optionally substituted up to two times by
 halogen or C₁₋₆ alkyl,

Y^3 is H;

X represents F;

15 n represents 0 or 1;

R^1 and R^2 each represents H;

R^3 represents

- C₁₋₆ alkyl,
 C₁₋₄ alkoxy,
20 CN, or
 N(R^1)₂ wherein the R^1 moieties are independent, or the R^1 moieties optionally
 are joined by a linker selected from the group consisting of CH(R^1),
 N(R^1), S, S(O), S(O)₂, and O, and taken together with the N to which
 they are attached, form a 5-6 membered nonaromatic heterocycle;

25 p represents 0 or 1;

q is 0;

L is a linker selected from

- O-(CH₂)₁₋₄- ,
 -S(O)₀₋₂-(CH₂)₁₋₄- ,
30 -N(R^1)-(CH₂)₁₋₄- ,
 -(CH₂)₁₋₄-O-(CH₂)₁₋₄- , and
 -N(R^1)-C(O)-(CH₂)₁₋₄- , and

G represents



wherein

R^5 represents H or C_{1-6} alkyl; and

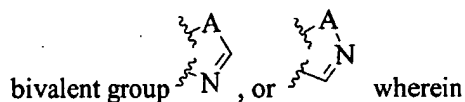
R^6 represents

C_{1-6} alkyl,

C_{5-6} cycloalkyl optionally substituted up to 2 times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy,

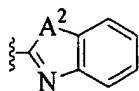
benzyl,

phenyl optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, $-\text{CO}_2\text{R}^1$, $-\text{C}(\text{O})\text{N}(\text{R}^1)_2$, $-\text{N}(\text{R}^1)_2$, or by a



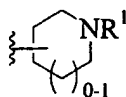
A is $\text{N}(\text{R}^1)$, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, or O, and

said bivalent group is connected to the phenyl ring at adjacent carbon atoms to form a fused 5-membered heterocycle, or

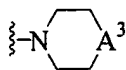


, wherein A^2 represents $\text{N}(\text{R}^1)$, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, or

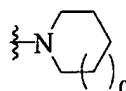
O,



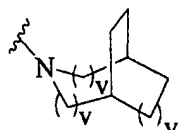
, optionally substituted up to 2 times by C_{1-3} alkyl, $(\text{C}_{1-3}$ alkoxy)(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl,



, optionally substituted up to 2 times by C_{1-3} alkyl, $(\text{C}_{1-3}$ alkoxy)(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl, and wherein A^3 represents $\text{N}(\text{R}^1)$, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, or O,



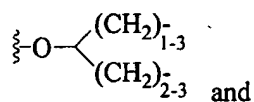
, optionally substituted up to 2 times by oxo, $(\text{C}_{1-3}$ alkoxy)-(C_{1-4} alkyl), $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, phenyl, or benzyl, or up to 4 times by C_{1-3} alkyl,



, optionally substituted up to 2 times by halogen, C₁₋₄ alkyl,
or C₁₋₄ alkoxy, and wherein
v is 0 or 1,

5 or

L represents



G represents



10

18. A compound of claim 1 wherein

Y¹ represents H;

Y² is selected from

15 C₁₋₆ alkyl, and

C₃₋₆ cycloalkyl optionally substituted by C₁₋₄ alkyl,

Y³ is H;

X represents F;

n represents 0 or 1;

20 R¹ and R² each represents H;

R³ represents

C₁₋₆ alkyl,

C₁₋₄ alkoxy, or

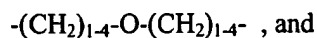
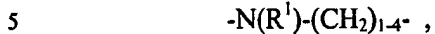
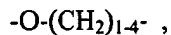
N(R¹)₂ wherein the R¹ moieties are independent, or the R¹ moieties optionally
are joined by a linker selected from the group consisting of CH(R¹),
N(R¹), S, S(O), S(O)₂, and O, and taken together with the N to which
they are attached, form a 5-6 membered nonaromatic heterocycle;

25

p represents 0 or 1;

q is 0;

L is a linker selected from



G represents



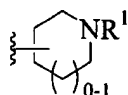
wherein

R⁵ represents H or C₁₋₆ alkyl; and

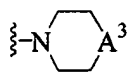
R⁶ represents

C₁₋₆ alkyl, or

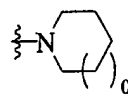
C₅₋₆ cycloalkyl optionally substituted up to 2 times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy,



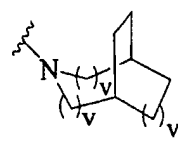
, optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl,



, optionally substituted up to 2 times by C₁₋₃ alkyl, (C₁₋₃ alkoxy)(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, and wherein A³ represents N(R¹), S, S(O), S(O)₂, or O,



, optionally substituted up to 2 times by oxo, (C₁₋₃ alkoxy)-(C₁₋₄ alkyl), C(O)OR¹, C(O)N(R¹)₂, phenyl, or benzyl, or up to 4 times by C₁₋₃ alkyl,



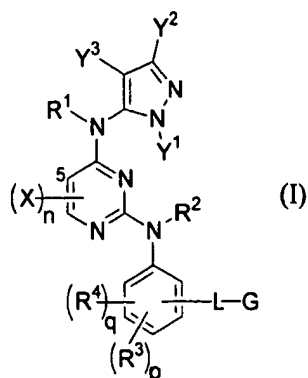
, optionally substituted up to 2 times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy, and wherein

v is 0 or 1.

19. A pharmaceutical composition comprising a compound of claim 1 and a

pharmaceutically acceptable carrier.

20. A method of inhibiting Src kinase receptors in a subject comprising contacting said
receptors with the compound according to claim 1.
- 5 21. A method for treating a disease associated with a src kinase in a subject, comprising
administering to said subject a therapeutically effective amount of a compound
according to claim 1, such that the disease is treated.
- 10 22. The method of claim 21 wherein said disease is cancer or osteoporosis.
23. A method for treating cancer in a subject, comprising administering to said subject a
therapeutically effective amount of a compound according to claim 1, such that the
cancer is treated.
- 15 24. The method of claim 23, wherein the cancer is selected from the group consisting of
breast cancer, colon cancer, pancreatic cancer, lung cancer, neural cancer, esophageal
cancer, gastric cancer, melanoma and Kaposi's sarcoma.
- 20 25. A method for treating a non-malignant proliferative disease in a subject, comprising
administering to said subject a therapeutically effective amount of a compound
according to claim 1, such that the non-malignant proliferative disease is treated.
26. A method for treating osteoporosis in a subject, comprising administering to said
25 subject a therapeutically effective amount of a compound according to claim 1, such
that the osteoporosis is treated.
27. A method for preparing a compound of formula (I)



wherein

Y^1 represents H, C_{1-4} alkyl, or phenyl optionally substituted up to three times by
halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

5 Y^2 and Y^3 are independently selected from

H,

C_{1-6} alkyl,

C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl,

phenyl optionally substituted up to three times by halogen, C_{1-4} alkyl, or

10 C_{1-4} alkoxy,

adamantyl,

CF_3 ,

a 5-6 membered heteroaromatic containing up to two heteroatoms selected

from N, O, and S, and optionally substituted up to two times by

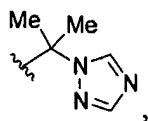
15 halogen or C_{1-6} alkyl,

$C(O)N(C_{1-4} \text{ alkyl})_2$,

$C(O)O(C_{1-4} \text{ alkyl})$,

CN,

halogen, and



20

or

Y^2 and Y^3 are joined and together represent a fused aromatic ring optionally
substituted up to two times by halogen, C_{1-4} alkyl, or C_{1-4} alkoxy,

X represents halogen or C₁₋₄ alkyl;

n represents 0, 1, or 2;

R¹ represents H or C₁₋₄ alkyl;

R² represents H or C₁₋₄ alkyl;

5 R³ represents

C₁₋₆ alkyl,

halogen,

C₁₋₄ alkoxy,

10 O-phenyl optionally substituted up to two times by halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, or di-(C₁₋₄ alkyl)amino,

CN,

15 N(R¹)₂ wherein the R¹ moieties are independent, or the R¹ moieties optionally are joined by a linker selected from the group consisting of CH(R¹), N(R¹), S, S(O), S(O)₂, and O, and taken together with the N to which they are attached, form a 5-6 membered nonaromatic heterocycle; p represents 0, 1, or 2;

R⁴ represents C₁₋₄ alkyl or halogen;

q represents 0, 1, or 2; or

20 R³ and R⁴ may be joined and taken together with the carbon atoms to which they are attached, form a 5-6 membered heteroaromatic ring containing up to two heteroatoms selected from N, O, and S, and which is optionally substituted up to two times by halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy,

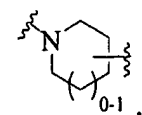
L is a linker selected from

-O-(CH₂)₁₋₄- ,



-S(O)₀₋₂-(CH₂)₁₋₄- ,

-N(R¹)-(CH₂)₁₋₄- ,



-(CH₂)₁₋₄-O-(CH₂)₁₋₄- ,

$-(CH_2)_{1-4}-$,
 $-C\equiv C-(CH_2)_{1-4}-$, or
 $-N(R^1)-C(O)-(CH_2)_{1-4}-$, and

G represents



5 NR^5R^6 ,

wherein

R^5 represents H, C_{1-6} alkyl, or C_{1-4} alkoxy- C_{1-4} alkyl; and

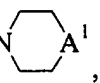
R^6 represents

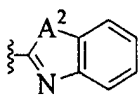
10 H,
 C_{1-6} alkyl,
 C_{1-4} alkoxy-substituted C_{1-4} alkyl,
 C_{5-6} cycloalkyl optionally substituted up to 2 times by
 halogen, C_{1-4} alkyl, or C_{1-4} alkoxy,
 C_{3-6} cycloalkyl-substituted C_{1-4} alkyl,
 15 benzyl,
 phenyl optionally substituted by halogen, C_{1-4} alkyl,
 C_{1-4} alkoxy, $-CO_2R^1$, $-C(O)N(R^1)_2$, $-N(R^1)_2$, or by a

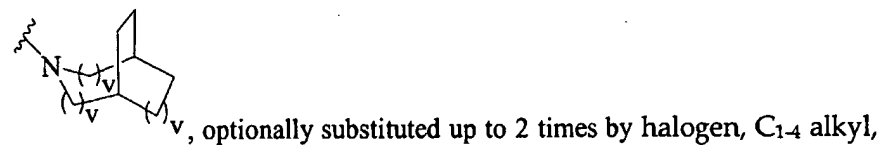
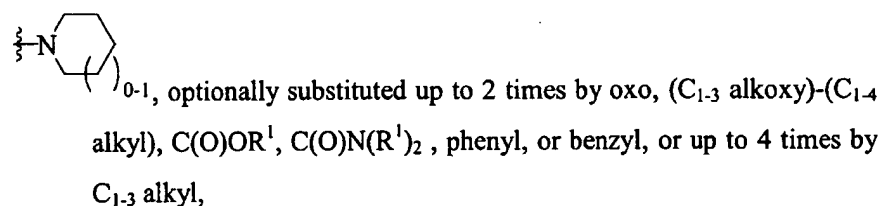
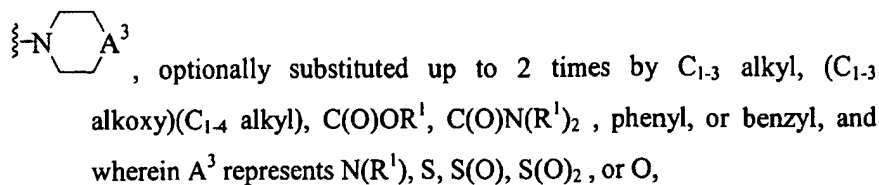
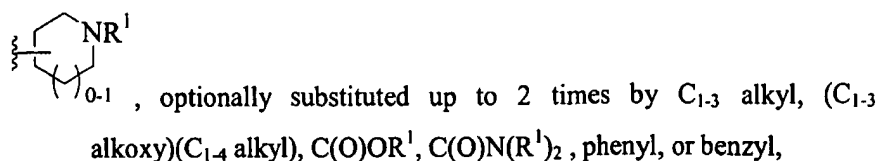
bivalent group  , or  wherein

A is $N(R^1)$, S, S(O), S(O)₂, or O , and

20 said bivalent group is connected to the phenyl
 ring at adjacent carbon atoms to form a
 fused 5-membered heterocycle,

$-(C_{1-4} \text{ alkyl})-N$  , wherein A^1 represents $N(R^1)$, S, S(O),
 S(O)₂ , or O, or

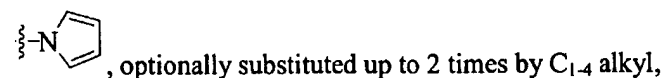
25  , wherein A^2 represents $N(R^1)$, S, S(O), S(O)₂ , or
 O,



10 or C₁₋₄ alkoxy, and wherein

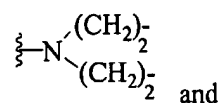
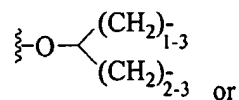
v is 0 or 1,

and

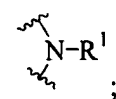


15 or

L represents

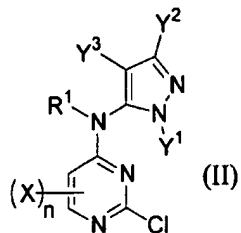


20 G represents

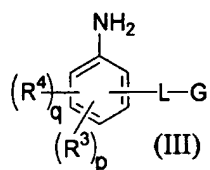


comprising

coupling a compound of formula (II)



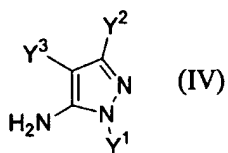
5 with a compound of formula (III)



, and, in the case where R² is an alkyl group, alkylating the resulting secondary amine, to yield a compound of formula (I);

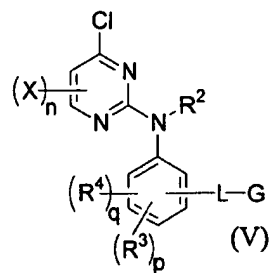
or

coupling a compound of formula (IV)



10

with a compound of formula (V)



and, in the case where R¹ is an alkyl group, alkylating the resulting secondary amine, to yield a compound of formula (I).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/30984

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/506 C07D401/14 C07D403/12 C07D403/14 C07D405/14
C07D409/14 C07D417/14 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 60816 A (AMGEN INC) 23 August 2001 (2001-08-23) page 72 -page 77; claims 1-5 page 25; table 1, compound 7 page 19, line 9 - line 11 ---	1-27
X	WO 00 39101 A (BREAU LT GLORIA ANNE ;PEASE JANET ELIZABETH (GB); ASTRAZENECA UK LT) 6 July 2000 (2000-07-06) page 123 -page 132; claims 1-8,11-14 ---	1-19, 23-27
X	WO 01 64655 A (BREAU LT GLORIA ANNE ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) page 59 -page 67; claims 1-10,12-17 ---	1-14,16, 17,19, 23-27
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

17 January 2003

Date of mailing of the international search report

04/02/2003

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Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/30984

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 64656 A (PEARSON STUART ERIC ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) page 52 -page 58; claims 1,2,4-8,10-15 ---	1-19, 23-27
X	WO 97 19065 A (CELLTECH THERAPEUTICS LTD ;DAVIS PETER DAVID (GB); MOFFAT DAVID FE) 29 May 1997 (1997-05-29) page 77 -page 80; claims 1-3,6,7,10 ---	1-19, 23-27
P,X	WO 02 062789 A (MILLER ANDREW ;KNEGTEL RONALD (GB); BEBBINGTON DAVID (GB); CHARRIE) 15 August 2002 (2002-08-15) page 321 -page 343; claim 1 page 328 -page 329; claims 9,11 page 331; claim 26 -----	1-27

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-27 (in part)

the compounds of the present formula (I) wherein L represents a linker selected from
-O-(CH₂)₁₋₄-, -O-cyclopentylene-, -O-cyclohexylene-,
-S(O)O-2-(CH₂)₁₋₄-, -N(R₁)-(CH₂)₁₋₄-, 1-pyrrolidinylene,
1-piperidinylene, -N(R₁)-C(O)-(CH₂)₁₋₄-,
-O-CH((CH₂)₁₋₃-)((CH₂)₂₋₃-), and 1,4-piperazinylene;

2. Claims: 1-27 (in part)

the compounds of the present formula (I) wherein L represents a linker selected from
-(CH₂)₁₋₄-O-(CH₂)₁₋₄-

3. Claims: 1-13 (in part), 16 (in part), 19-27 (in part)

the compounds of the present formula (I) wherein L represents a linker selected from
-(CH₂)₁₋₄-

4. Claims: 1-12 (in part), 19-27 (in part)

the compounds of the present formula (I) wherein L represents a linker selected from
-(1,2-ethinediyl)-(CH₂)₁₋₄-

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/30984

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/30984

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